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SYMPOSIUM

ON

HYDROXYPHENAMATE

A SCIENTIFIC MEETING

held under the auspices of

DEPARTMENT OF PSYCHIATRY
WOMAN'S MEDICAL COLLEGE OF PENNSYLVANIA

at

DENNIS HOTEL
ATLANTIC CITY, NEW JERSEY

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Hydroxyphenamate is available from the Armour Pharmaceutical Co., Kankakee, Illinois, under the trade name Listica®.

DISEASES *of the* Nervous System

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Symposium on Hydroxyphenamate

INTRODUCTION

B. E. McLaughlin, M. D.*

As a representative of the Department of Psychiatry of the Woman's Medical College of Pennsylvania, I am honored to welcome the assembled group to this symposium being held under the auspices of our Department. The purpose of this meeting is to bring together, as concisely and completely as possible, the pre-clinical and clinical work done to date, on an important new psychopharmacological compound, hydroxyphenamate. It is our hope that each of us will go away from this meeting with a clearer understanding of where this particular compound fits into the armamentarium of present day treatment. Through this meeting, each of us will gain the meaning of the experimental work viewed against the background of the sum total of the studies reported here.

I bring to you the greetings of Dr. Marion Fay, President and Dean of the Woman's Medical College, who has asked me to express her pleasure that this meeting could be held under our auspices. We hope that all of you will now or at a future opportunity visit our institution which is the only medical college in the western hemisphere devoted exclusively to the training of the woman for the degree in medicine.

We wish to thank the Armour Pharmaceutical Company for the many courtesies extended to our College in setting up and expediting this symposium.

To set the scene for this meeting, consider briefly the progress that has been made in the last generation in the treatment of mental and emotional disorders. Today there is great interest in the psychic components of various diseases which until recently were considered to be largely organic. This interest derived from the tremendous progress made over the past generation in research and treatment of the true mental condition. Insulin therapy for schizophrenia is not yet a generation old. Professor Cerletti gave the first electro-convulsive therapy in the 1930's. Almost unbelievably, the whole concept of the psychopharmacologic drugs is only about a decade from its birth. With the tremendous advances made by these therapeutic measures in the field of severe mental illness, it was natural that physicians of every specialty and general practice should have begun to consider the emotional and mental elements of conditions other than those of a purely psychiatric nature. For the first time, effective tools were available for patient care on a broad basis. As a teacher of psychiatry, I have been truly amazed at the advances made over the past generation in the understanding of psychological concepts by men other than physicians. I am sure that much of this important breakthrough has been sparked by the advent of psychopharmacology.

These psychopharmacologic drugs have also caused a growing public awareness of the social importance of mental illness. There are about as many hospital beds occupied in the United States by patients suffering from mental illness as from all other physical illnesses combined. In addition, a large proportion of patients who consult medical practitioners do so because of symptoms which, to a large extent, are psychogenic in nature.

How appropriate then, that we should gather here, representing internal medicine and its specialities, neurology, dermatology, allergy, cardiology, and general practice, as well as psychiatry and psychology to investigate and test against each other's experiences, a new psychopharmacologic agent which has had its initial testing not only on psychotic and psychoneurotic patients, but also, on patients from each of

*Head, Department of Psychiatry, Woman's Medical College of Pennsylvania.

the special spheres of what my professors would certainly have termed organic medicine.

In a meeting in which there is a discussion of many different compounds and attitudes, we tend to get somewhat lost in the divergent approaches in discipline and therapy. But in this meeting, we have one day to discuss a drug which all of us have investigated in our respective areas. Each of us can present his own philosophic approach to the treatment of his patients, and each of the others will know that we are at least talking from the same starting point — a specific drug. Each man can portray his therapeutic objectives, which differ from discipline to discipline; each man can see the dose range useful in other areas; each man can understand and appreciate the other's criteria of therapeutic judgment.

Let us discuss Listica not only as an agent but also what medicine, in its various branches, is really concerned with—patient care. As chairman of the meeting, I will do what I can to keep the discussion on the track of this broad, philosophic approach to medicine and combat the tendency that all of us have to drift off into the detailed abstractions that go with any specialized scientific discipline.

Let us then, for this day's discussion, and in our future practice relationships, try to forget that we are principally psychiatrists, neurologists, internists, dermatologists, and remember that we are physicians, interested in the total care of man. With this in mind, I have asked that each man limit his paper to the true essence of his experiment. I hope there will be much time for general discussion and a crossover of disciplines. We can all benefit fully from the experience of others possessing skills we ourselves cannot hope to acquire and experiences beyond our individual areas. In this way we may not only go away from this meeting with a fuller understanding of this drug and others of a similar type, but with a broader understanding of what the total handling of the ill man (organic, psychological, social, economic, cultural) can and must be in our rapidly and advancing world of medicine.

Chemistry of Hydroxyphenamate*

CHARLES D. BOSSINGER, PH. D.†

Hydroxyphenamate is the product of a central nervous system drug program at Armour Pharmaceutical Company. This program was established with the goal to find compounds which have useful therapeutic action on the central nervous system. These compounds include tranquilizers, sedatives, muscle relaxants and anti-epileptics as well as drugs with action due to central control (e.g. anti-obesity drugs.).

A definite aim has been to produce substances that have a specific action on the central nervous system as opposed to a general action. As a means of obtaining drugs of this character, a number of animal tests have been developed by our pharmacology department. The principal ones, the metrazol battery and electroshock assays, are described by J. W. Bastian, et al.[1,2]

Table I enumerates parts of these assays. Each assay in the battery assay is carried out on the same mouse. This tends to minimize the effect of biological variability. The arrows indicate that an increase or decrease is recorded in these parameters and the + – indicates that the blocking or failure to block these parameters is recorded.

TABLE I

Animal Screen in CNS Drugs

A.	Battery Assay	
	1. Motor Activity	↑ ↓
	2. Body Temperature	↑ ↓
	3. Metrazol Threshold	↑ ↓
	4. Blocking of Extensor Tonus	+ –
	5. Pupil Diameter	↑ ↓
B.	Electroshock Assay	
	1. Threshold	↑ ↓
	2. Extensor Tonus	+ –

These assays are used to evaluate all the drugs synthesized by the organic chemistry CNS group, as well as a large number of drugs known to have therapeutic effects on the central nervous system. These data together with other factors determine which drugs are to be clinically tested.

Factors involved in selection of compounds for clinical trial are given in Table II.

TABLE II

Selection of Compounds for Clinical Trial

Factors Involved

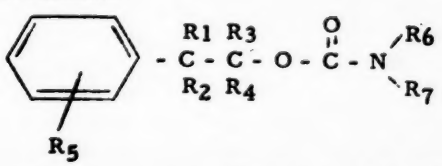
1. Compare Profiles with Known Compounds
2. Select Compounds with Similar Profiles
3. Select Compounds with Distinct Profiles
4. Economy of Synthesis
5. Patent Status

Compounds which have profiles similar to drugs with known therapeutic action are selected for further consideration for clinical testing. Compounds are also selected that have distinct profiles e.g. effect only one of the assays. After compounds have been selected on this basis, a further selection is made on the basis of ease and economy of synthesis and the status of the compounds in relation to patents.

The compounds selected for clinical testing are then subjected to extensive acute and chronic animal toxicity studies. Then controlled human pharmacology studies are carried out before they are submitted for more general testing.

Hydroxyphenamate, as well as the other drugs in our central nervous system drug clinical testing program, have gone through this method of testing.

Using this type of evaluation, one series of chemical compounds seemed to have the most interesting pharmacological activity. One of the reasons for this interest was that any change in the molecule caused a change in specificity for the central nervous system. These compounds were the 2-phenylethyl carbamates.

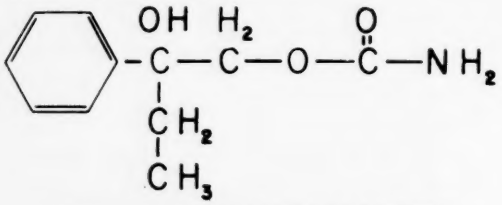


This represents the general formula for this series. Several hundred compounds have been made varying one or more of the R groups shown in this formula. A number of these compounds are presently being tested clinically for their effects as tran-

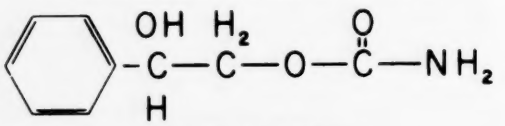
*Trade name hydroxyphenamate is Listica®—manufactured by Armour Pharmaceutical Company, Kankakee, Illinois.

†Head, Organic Chemistry Department, Armour Pharmaceutical Company, Kankakee, Illinois.

quilizers, sedatives, muscle relaxants and appetite depressants. The two compounds from this series that had sufficient activity to warrant extensive clinical study are hydroxyphenamate and styramate.‡



HYDROXYPHENAMATE



STYRAMATE

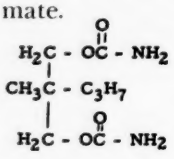
It can be seen that hydroxyphenamate differs from styramate by having an ethyl group replacing the hydrogen on the carbon adjacent to the benzene ring. As with most compounds in this series this replacement causes a marked change in the specificity of hydroxyphenamate for the central nervous system. Hydroxyphenamate is a mild tranquilizer as will be shown by the papers following on this symposium. Styramate is a specific muscle relaxant.[3,5] It also causes a marked change in the chemical properties of the drug. Table III shows that melting point, water solubility, chloroform solubility and infra-red spectra are markedly changed by this slight change in structure.

TABLE III

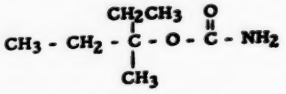
Chemical Differences

	Hydroxyphenamate	Styramate
Melting Point	56-8	114-16
Water Solubility	about 2.5%	very slight
Chloroform Solubility	good	insoluble
Infra Red Spectrum Carbonyl Bond	5.8 microns	6.0 microns

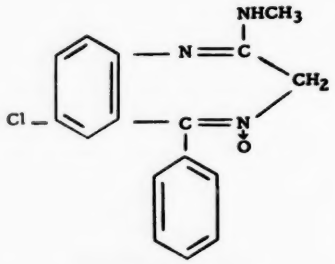
Furthermore, hydroxyphenamate, is a distinctly new structure. It differs markedly from those drugs now marketed as anti-anxiety agents. The structure of some of these agents is given below. Hydroxyphenamate is the only one of the carbamate tranquilizers to contain a phenyl group. It is also the only hydroxycarbamate in this class of drugs. Meprobamate is a dialkyl substituted 1, 3 dicarbamate while emylcamate is a branched chain monocarbamate.



Meprobamate



Emylcamate



Chlordiazepoxide

R_1=hydrogen, hydroxyl, aryl, acyl
R_2, R_3, R_4 = hydrogen, alkyl, aryl
R_5 = alkyl, aryl, nitro, halogen, alkoxy, etc.
R_6, R_7 = alkyl, aryl, cycloalkyl

This phenyl group might possibly explain the longer duration of action of hydroxyphenamate. While chlordiazepoxide contains aromatic groups it is a three ring structure unrelated to hydroxyphenamate.

In summary, we believe from our studies that the phenyl group, the ethyl group, and the hydroxy group of hydroxyphenamate all contribute to the maximum therapeutic activity, specificity of action, good duration of action and a minimum of side effects.

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‡Styramate is manufactured by Armour Pharmaceutical Company, Kankakee, Illinois, under the trade name Sinaxar®.

Pharmacology and Toxicology of Hydroxyphenamate (Listica)

J. W. Bastian, Ph. D.* and G. R. Clements, Ph. D.*

Hydroxyphenamate (2-hydroxy-2-phenylbutyl-carbamate), a new agent effective in the treatment of anxiety and tension, is chemically unrelated to any other current psychotherapeutic drug. In clinical practice, hydroxyphenamate exerts consistent therapeutic effects in the relief of anxious patients. It is a potent drug, possessing what is thought to be an optimum duration of action, and appears to be unusually free from side effects including those common to its predecessors.

This paper summarizes the animal pharmacological data on CNS and non-CNS effects of hydroxyphenamate, as well as results of subacute and chronic toxicity studies. For most of the studies, results with standard drugs are shown for comparison.

CNS Effects

Mouse Screening Studies

Figure 1 shows some of the mouse screening results for hydroxyphenamate. The effects of meprobamate, chlordiazepoxide and chlorpromazine are shown for comparison. All drugs were administered orally in 1% pectin and effects were measured at 30, 60 and 120 minutes after drug administration. The data shown at zero time are for untreated controls run simultaneously. Two or 3 dose levels were run for each of these drugs, but for comparative purposes the results for only one dose level for each drug are shown here. Doses chosen for illustration were those showing as nearly equal over all effects as possible. Details of the assay methods employed have been described elsewhere.[2,3]

In these studies, special efforts have been taken to make all data obtained comparable. Thus, all mouse results shown in Figure 1 involve the same strain, same sex (female) and the same body weight range. For any given drug, the same dose and same route of administration were employed in all assays. In many cases the various measurements were made on the same animals. In this way, we hope to best demonstrate differences in drug specificity.

It is apparent from the data in Figure 1 that the effects of hydroxyphenamate, meprobamate and chlordiazepoxide are generally similar and that all differ appreciably from chlorpromazine.

Comparing the three anti-anxiety drugs, hydroxyphenamate is found to be intermediate to the other two in overall potency. With regard to duration of action, these and other data indicate that hydroxyphenamate is longer acting than meprobamate and shorter acting than chlordiazepoxide. For example, with hydroxyphenamate (100 mg/Kg), Metrazol threshold elevation was found to have returned to 36% of maximal elevation by six hours after drug administration. In contrast, chlordiazepoxide (50 mk/Kg) exhibited 93% of maximal effectiveness at this time. On the other hand, the effect of meprobamate (100 mg/Kg) was down to 20% of maximal only two hours after drug administration. We believe this represents a distinct advantage for hydroxyphenamate, since this drug possesses an action that is neither too fleeting nor so long that cumulation and the need for subsequent dosage reduction occur.

Certain differences in specificity between the three anti-anxiety drugs are apparent in these mouse screening results. For example, hydroxyphenamate is relatively more potent against the tonic extensor phase of the Metrazol seizure than is either chlordiazepoxide or meprobamate. The electroshock threshold elevating effect of hydroxyphenamate is much greater than that of meprobamate. Hydroxyphenamate affords better protection against Metrazol death than the other drugs. Hydroxyphenamate was found to cause less impairment of coordination than meprobamate or chlordiazepoxide. Meprobamate and hydroxyphen-

*From Dept. of Pharmacology, Armour Pharmaceutical Company, Kankakee, Illinois.

Presented in part to the American Society for Pharmacology and Experimental Therapeutics, Miami, August, 1960. (See reference 1).

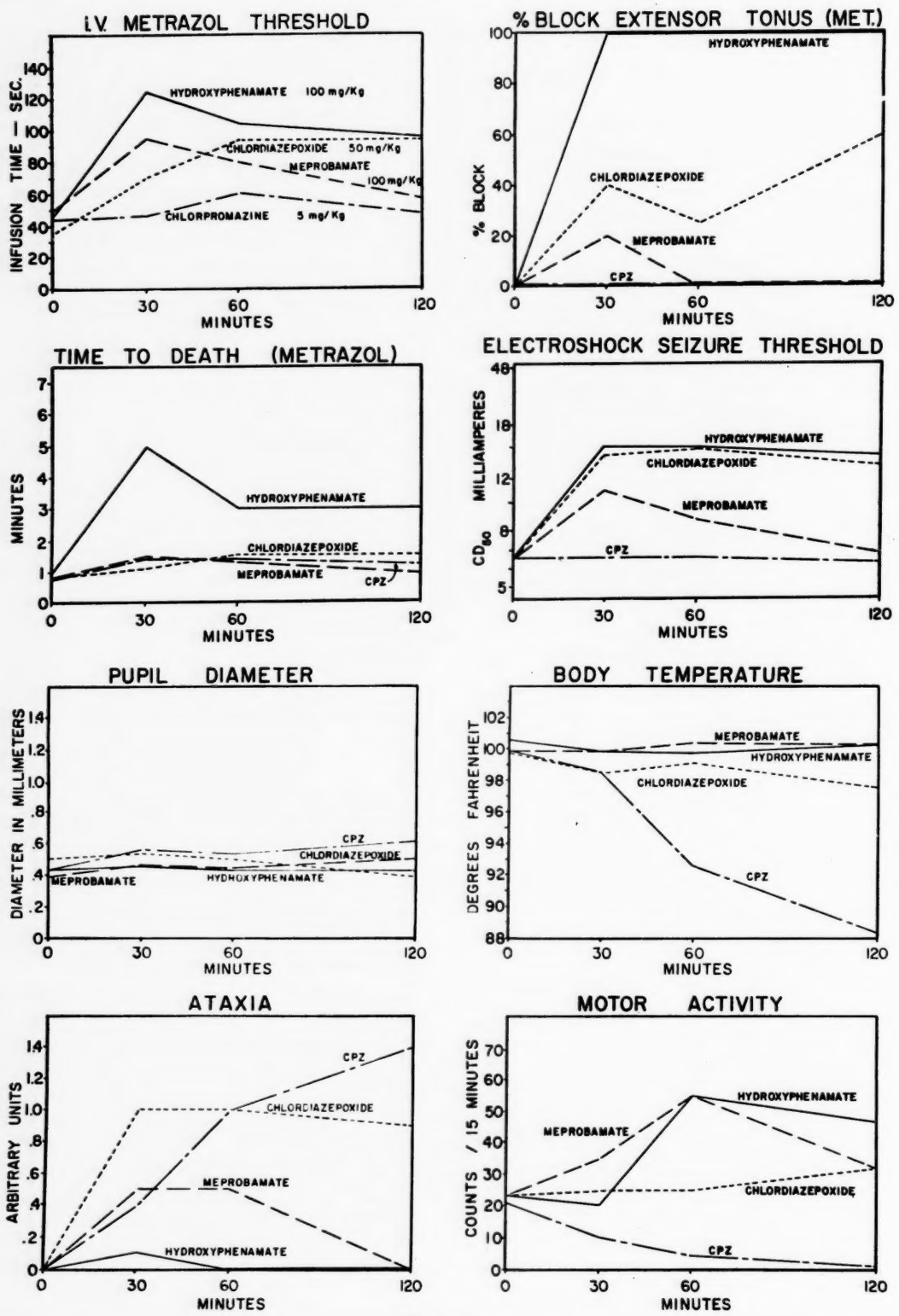
I.V. METRAZOL THRESHOLD
INFUSION TIME — SEC.
HYDROXYPHENAMATE 100 mg/Kg
CHLORDIAZEPOXIDE 50 mg/Kg
MEPROBAMATE 100 mg/Kg
CHLORPROMAZINE 5 mg/Kg
MINUTES
% BLOCK EXTENSOR TONUS (MET.)
% BLOCK
HYDROXYPHENAMATE
CHLORDIAZEPOXIDE
MEPROBAMATE
CPZ
MINUTES
TIME TO DEATH (METRAZOL)
MINUTES
HYDROXYPHENAMATE
CHLORDIAZEPOXIDE
MEPROBAMATE
CPZ
MINUTES
ELECTROSHOCK SEIZURE THRESHOLD
MILLIAMPERES
CD50
HYDROXYPHENAMATE
CHLORDIAZEPOXIDE
MEPROBAMATE
CPZ
MINUTES
PUPIL DIAMETER
DIAMETER IN MILLIMETERS
CPZ
CHLORDIAZEPOXIDE
MEPROBAMATE
HYDROXYPHENAMATE
MINUTES
BODY TEMPERATURE
DEGREES FAHRENHEIT
MEPROBAMATE
HYDROXYPHENAMATE
CHLORDIAZEPOXIDE
CPZ
MINUTES
ATAXIA
ARBITRARY UNITS
CPZ
CHLORDIAZEPOXIDE
MEPROBAMATE
HYDROXYPHENAMATE
MINUTES
MOTOR ACTIVITY
COUNTS / 15 MINUTES
HYDROXYPHENAMATE
MEPROBAMATE
CHLORDIAZEPOXIDE
CPZ
MINUTES

Figure 1

amate tended to increase spontaneous activity under our assay conditions, whereas chlordiazepoxide had no effect. None of these three anti-anxiety drugs had a significant effect on pupil diameter or body temperature. In contrast, chlorpromazine caused a marked depression of body temperature.

Rat Screening Studies

To determine the effects of hydroxyphenamate in rats, the drug was administered orally in 1% pectin to females weighing approximately 120 grams. Measurements of drug effects on Metrazol threshold, extensor tonus, motor activity, body temperature and ataxia were made in ways similar to those described above for mice. The results were very similar to those obtained with mice. At 100 mg/Kg *per os,* Metrazol threshold elevation was observed and the tonic extensor phase of the Metrazol seizure was blocked by hydroxyphenamate. Body temperature was not altered and only a slight degree of ataxia was detected. Motor activity was elevated.

Cat Studies

In the cat, the onset of central nervous system effects usually occurs about 15 minutes after oral administration of hydroxyphenamate, attesting to the rapid oral absorption. The gross behavioral effects of the drug are as follows: At oral doses below 80 mg/Kg no alterations in behavior are noted except for possible quieting. At 80 mg/Kg, or just above, the cats become ataxic. Loss of righting-reflex occurs at 120 to 160 mg/Kg, but heart rate and breathing are normal at this dose. At higher doses, anesthesia ensues. No vomiting, diarrhea, salivation, tremors or other untoward effects are observed and, in fact, the anesthesia can not be differentiated from that caused by phenobarbital.

In order to evaluate the effects of hydroxyphenamate on the electroencephalogram of cats, chronic, bipolar, screw electrodes were implanted to permit subsequent recording of drug effects in the absence of anesthesia. Hydroxyphenamate was administered by gavage in repeated doses of 40 mg/Kg every 15 minutes to four cats. Ten minutes after each drug treatment, electroencephalographic tracings were made and behavioral effects of the drug were noted. Figure 2 shows results for one cat typical of those obtained.

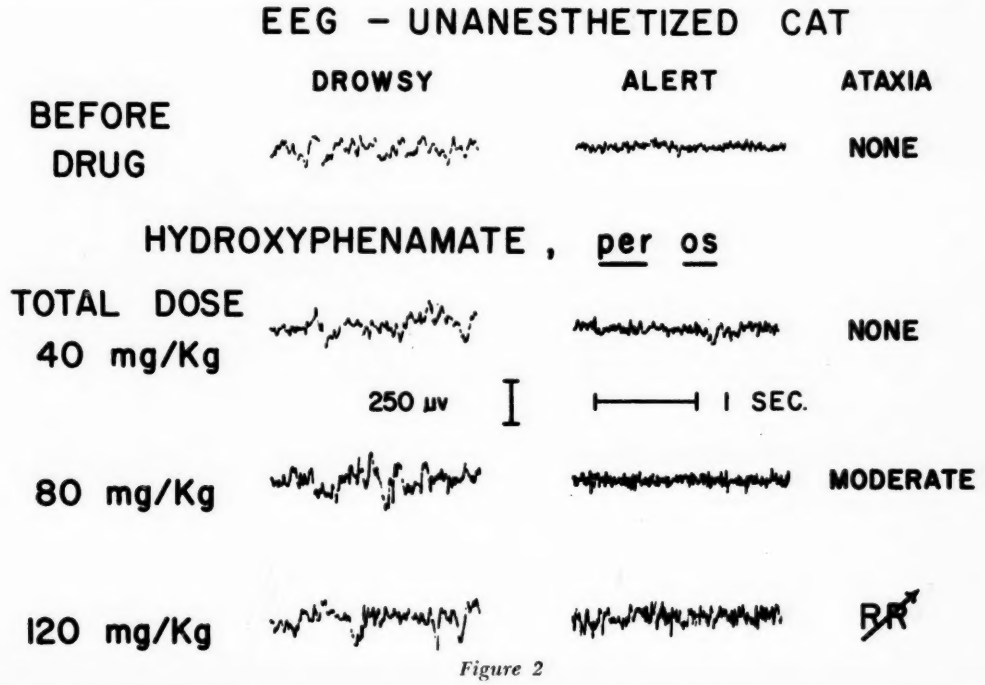

Figure 2

Comparison of the drowsy and alert records following the 120 mg/Kg total dose indicates that the arousal response to sensory stimulation was not blocked, even though the animal had lost the ability to right itself. The pattern of the aroused EEG is clearly altered, however, and exhibits higher voltage, more spike-like activity than normal.

Chronic spinal cats were used in an evaluation of effects on spinal polysynaptic transmission. The animals were held in a special apparatus which permitted continuous recording of the flexor reflex of one hind leg. Periodic electrical stimulation via needles implanted in the foot elicited the flexor reflex. Drugs were administered by gavage. Hydroxyphenamate caused a mild depression of the flexor reflex at 80 mg/Kg and a severe depression at 160 mg/Kg. Both phenaglycodol and mephenesin exceeded hydroxyphenamate in potency on this assay. It is concluded that hydroxyphenamate causes a definite, but not marked depression of spinal polysynaptic transmission.

Effects in the Monkey

Dr. E. F. Domino at the University of Michigan has administered hydroxyphenamate to monkeys (Macaca mulatta) for determination of gross behavioral effects. At 50 mg/Kg, intramuscularly, there appeared to be a slight reduction of aggressiveness. No ataxia or sleepiness were observed. At 150 mg/Kg, a definite "slowing down" was noted. Aggression was reduced but not eliminated, and the monkeys exhibited an unusual tendency to hang from one spot. The animals were not ataxic but tended to slip upon alighting following a jump. There appeared to be muscle weakness but no drowsiness.

Non-CNS Effects

Cat Blood Pressure

Studies of the effects of hydroxyphenamate on blood pressure and on the EKG were made in four phenobarbitalized cats. Hydroxyphenamate was administered intravenously in repeated doses of 10 mg/Kg. The injections were given every 30 minutes until death of the animal, and recordings of EKG (Leads I, II and III) and arterial blood pressure were made at established intervals. The total dose of hydroxyphenamate needed to kill the cats averaged 280 mg/Kg (in addition to the full anesthetic dose of phenobarbital). Transient depressor responses of moderate amplitude followed each injection of the drug. However, pressures returned to near the pre-injection level in all cases, within the 30 minute period before the next injection. Cardiac slowing accompanied the depressor re-

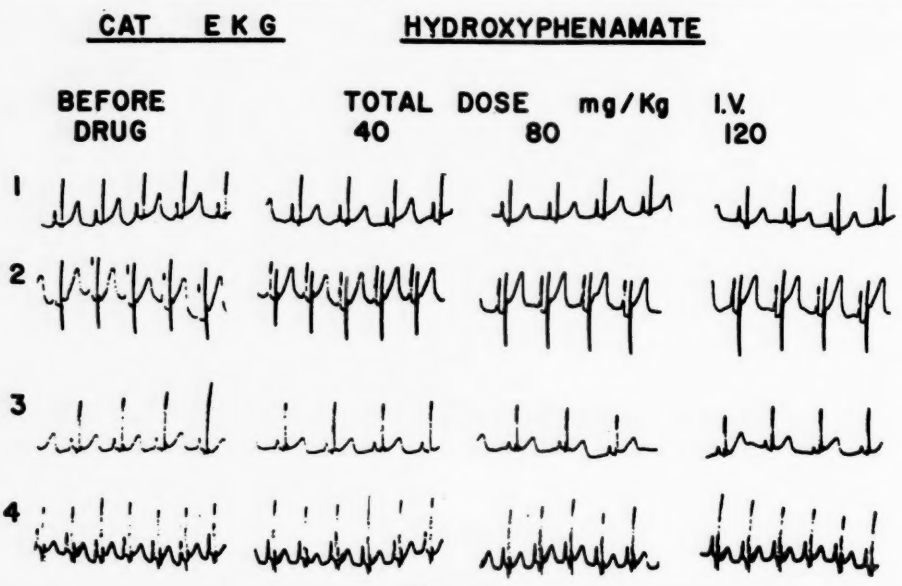

Figure 3

TABLE I

Rat Blood Pressure

Drug	*Intravenous Dose mg/Kg*	*EFFECT ON:* *Blood Pressure*	*2-20 μg/Kg Epinephrine Pressor*	*.01-10 μg/Kg Acetylcholine Depressor*
Hexamethonium	20	Depression	0	0
Phenoxybenzamine	10	Depression	Block	Partial Block
Atropine SO_4	5	0	0	Block
Hydroxyphenamate	100	0	0	0

0 = No Effect.

sponses but this also showed good recovery during the interinjection interval. Figure 3 shows the EKG tracing (Lead II) for the four cats for total doses up to 120 mg/Kg. No EKG changes attributable to the drug were observed except those associated with the cardiac slowing described above. Death was apparently caused by respiratory failure.

Rat Blood Pressure

Rat blood pressure experiments were carried out to determine if hydroxyphenamate alters blood pressure responses to epinephrine and acetylcholine. Rats were anesthetized with urethane, and carotid blood pressure was recorded by means of a strain gauge and an ink writing polygraph. The vasoactive drugs were administered intravenously before and after the intravenous administration of hydroxyphenamate. Atropine, phenoxybenzamine and hexamethonium were run as standards for comparison with hydroxyphenamate. The results, shown in Table I, indicate that hydroxyphenamate does not possess significant adrenolytic or anticholinergic effects. In addition, the lack of effect of hydroxyphenamate on arterial pressure indicates that the drug does not possess ganglionic blocking properties.

Other Autonomic Studies

Several other types of experiments have been carried out to determine the effects of hydroxyphenamate on the autonomic nervous system. Earlier, in presenting the mouse screening data, we pointed out the lack of effect of hydroxyphenamate on pupil diameter and body temperature. Table II shows the effect of representative autonomic drugs on these endpoints under our assay conditions. The lack of effect of hydroxyphenamate on these endpoints is therefore evidence of the absence of autonomic effects of this drug.

In addition to testing the systemic effects of hydroxyphenamate in mice, the drug was also instilled into the eyes of mice. A 3% concentration of the drug in saline was employed. This is about the limit of water solubility of the drug at room temperature. Table III shows the results in comparison to the effects produced by atropine and physostigmine in much smaller concentrations. The lack of effect of hydroxyphenamate on the mouse pupil indicates absence of cholinergic and anticholinergic effects.

Smooth muscle bath studies were conducted using the guinea pig ileum further to investigate the pharmacology of hydroxyphenamate. This drug, as well as appropriate standard drugs, was tested against the spasmogens acetylcholine, $BaCl_2$ and histamine. Concentrations of the drugs (μg/ml final bath) which inhibited contractions 50% are shown in Table IV. The results indicate that hydroxyphenamate does not possess significant inhibitory activity against any of these spasmogens.

TABLE II

Effects of Autonomic Drugs in Mice

Type	*Example*	*Pupil Diam.*	*Body Temp.*
Cholinergic	Physostigmine	↓	↓
Anti-Cholinergic	Atropine	↑	0
Adrenergic	Ephedrine	↑	↑
Adrenolytic	Phenoxybenzamine	0	↓
Ganglion Block	Hexamethonium	↑	↓
	Hydroxyphenamate	0	0

TABLE III

Mouse Pupil, Local

Drug	*Conc. mg/ml*	*Pupil Diameter mm's*
Atropine SO_4	0.1	2.1 (maximal)
Physostigmine SO_4	1	.1 (minimal)
Hydroxyphenamate	30	.5 (no effect)

TABLE IV

Smooth Muscle Bath (Guinea Pig Ileum)

	SPASMOGEN		
	ACh	$BaCl_2$	*Histamine*
Antagonist	0.25 μg/ml	100 μg/ml	0.2 μg/ml
Atropine SO_4	0.04	—	—
Papaverine	—	7	—
Diphenhydramine	—	—	0.2
Hydroxyphenamate	600	500	600

μ/ml, final conc. in bath

The effects of hydroxyphenamate against edema induced by serotonin and histamine were studied using the rat foot technique. Edema was induced by injection of histamine or serotonin into the plantar area of the rat's right hind foot. Necropsy was performed 30 minutes later to ascertain the difference in weight between the treated and untreated hind feet. Hydroxyphenamate, LSD and diphenhydramine were administered systemically 30 minutes prior to injection of serotonin or histamine. The results are shown in Table V. It is clear that LSD has inhibited serotonin edema and that diphenhydramine has inhibited histamine edema, but that hydroxyphenamate has not significally inhibited either type of response.

TABLE V

Rat Foot Edema – % Inhibition

			Inflammatory Agent	
	Dose	*Route*	*Sero-tonin*	*Hista-mine*
Antagonist	*mg/Kg*		(2 μg)	(500 μg)
LSD	1	PO	73%	—
Diphenhydramine	10	SQ	—	32%
Hydroxyphenamate	100	PO	−6%	−16%

Effect on Coagulation

In vitro studies of the effect of hydroxyphenamate on coagulation were carried out with recalcified rabbit plasma. No effects were obtained at the highest concentration tested, 12 mg/ml plasma.

Hemolytic Effect

Other studies were conducted using citrated whole rabbit blood to determine if hydroxyphenamate has any tendency to cause hemolysis. Again very high concentrations were tested. No effect was observed at levels of 3 mg/ml blood, or below. At 6 6 mg/ml a trace of hemolysis was detected. This level is considerably higher than any plasma level which would be expected to be encountered clinically, however.

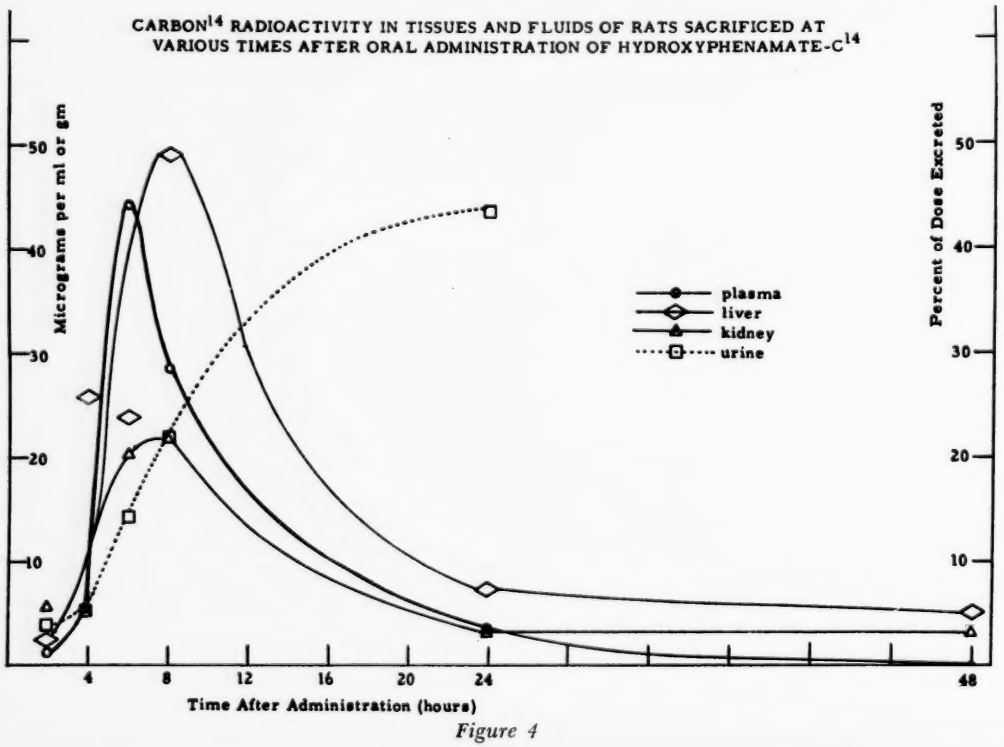
CARBON14 RADIOACTIVITY IN TISSUES AND FLUIDS OF RATS SACRIFICED AT VARIOUS TIMES AFTER ORAL ADMINISTRATION OF HYDROXYPHENAMATE-C14
Micrograms per ml or gm
Percent of Dose Excreted
plasma
liver
kidney
urine
Time After Administration (hours)

Figure 4

Metabolic Studies

Experiments were carried out by the Nuclear Science and Engineering Corporation of Pittsburgh using C^{14} ring-labelled hydroxyphenamate to learn something of the metabolic fate of the drug in rats. The dose was 25 mg/Kg, and it was administered by the oral route. Animals were sacrificed at 2, 4, 6, 8, 24 and 48 hours post administration. Blood was taken by heart puncture just before sacrifice. Determinations of radioactivity were made on liver, kidney, plasma, urine and feces. The results are shown in Figure 4. Peak plasma, liver and kidney levels of radioactivity were reached at 6 to 8 hours after administration. Thereafter, the levels declined rapidly. Approximately 40% of the administered radioactivity was excreted in the urine by 24 hours and 10% was excreted in the feces.

Toxicity Studies

Table VI shows the acute oral LD_{50}'s for hydroxyphenamate, meprobamate and chlordiazepoxide in mice. The drugs were administered in 1% pectin and the mice were observed for one week for determination of percent mortality. The intravenous LD_{50} of hydroxyphenamate in mice was found to be 425 ± 14 mg/Kg. For this study, the drug was administered in saline over a 10 second interval via the tail vein.

TABLE VI

Acute Oral $LD_{50} \pm$ S. E.

Hydroxyphenamate	830 ± 25
Chlordiazepoxide	995 ± 52
Meprobamate	1100 ± 79

One month subacute toxicity studies were done in rats, dogs, cats and rabbits. Administration was done by the oral or subcutaneous routes. In the cat studies, a mild inhibition of growth was observed which may have been caused by hydroxyphenamate. Some ulceration at the site of subcutaneous injection was seen in the rat studies. With these relatively minor exceptions, there were no indications from any of the other observations, including gross and microscopic examination of tissues, as well as hematological studies, of any toxic effect of hydroxyphenamate.

A six months' study of hydroxyphenamate was carried out with beagles to gain information on the possible toxic effects of chronic adminstration of the drug. Doses of 140, 200 and 320 mg/Kg were administered orally in capsules once daily. Only at the highest dose level, 320 mg/Kg, (an amount about 10 times above the highest recommended human dose) were any changes observed. These consisted of apparent increases in weight of liver, adrenals and thyroid. The absence of microscopic changes in these organs, however, negates the significance of organ weight changes. There were no macroscopic or microscopic changes in any organs or tissues of the dogs attributable to the drug at any of the dose levels studied.

Hydroxyphenamate was administered for 12 months to Sprague-Dawley rats to obtain additional information on the effects of chronic administration of the drug. Doses of 160, 320 and 640 mg/Kg per day were administered by gastric intubation. A high incidence of mortality occurred at the highest dose level. This dose was very near the acute LD_{50} in rats, however, and is about 20 times the maximum recommended human dose. Indications are that these deaths resulted mostly from chronic murine pneumonia, secondary to profound central nervous system depression. At lower doses, minor organ and body weight changes were seen. These changes are poorly dose related, however, and because of the complete absence of microscopic changes are not considered indicative of possible toxic effects of the drug. Hematologic findings were negative at all dose levels.

On the basis of the results of these subacute and chronic animal toxicity studies, hydroxyphenamate was expected to be safe, at the recommended dose levels, for prolonged administration to humans. Subsequent clinical use has confirmed this expectation.

Summary

Hydroxyphenamate is a new compound, chemically unique, possessing specific central nervous system effects. It is rapidly absorbed following oral administration and possesses what is believed to be an optimum duration of action. A variety of pharmacological studies indicate that hydroxyphena-

mate has no significant autonomic effects, or other undesirable actions upon acute administration of therapeutic dose levels. There is no evidence to indicate that the drug significantly depresses or stimulates appetite. Comparative studies in mice suggest that hydroxyphenamate may cause less ataxia than comparable drugs. Studies involving chronic administration to rats and beagles indicate that hydroxyphenamate is not expected to cause toxic effects on repeated administration for long periods.

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DISCUSSION OF DR. BASTIAN'S PAPER

Moderator: Are there any questions on Dr. Bastian's presentation?

Question:

Dr. Alexander: Would Dr. Bastian comment again on the evidence regarding the lack of an adrenergic effect?

Answer:

Actually, there are two things involved; first, the absence of a direct adrenergic effect of hydroxyphenamate, and second, the absence of an adrenergic blocking effect. With regard to the first point, the lack of a pressor effect of the drug following intravenous administration to cats and rats is some evidence. Also, in the mouse pupil diameter studies, the lack of effect of hydroxyphenamate applied locally or administered systemically is evidence of absence of adrenergic effect. Lack of adrenergic blocking effect is shown by the inability of hydroxyphenamate to block epinephrine pressor responses in rats.

Question:

Dr. Alexander: Does this mean that it leaves the hypothalamic area unaffected?

Answer:

Not necessarily. The test I just mentioned would be for peripheral autonomic effects rather than central effects. On the other hand, the nearly complete lack of effect of hydroxyphenamate on a variety of mechanisms under autonomic control suggests that the drug has no significant actions on central autonomic mechanisms in the hypothalamus.

Question:

Dr. Lunde: What dosage range of Metrazol was used in the mouse studies?

Answer:

The concentration employed was 10 mg/ml, and it was infused at the rate of 0.2 ml/minute into the tail vein. This results in a maximal seizure in about 50 seconds in untreated mice. A dose of hydroxyphenamate of 100 mg/Kg would raise this threshold to about 125 seconds, or about 2½ fold. This is a very marked prolongation of time to seizure.

Question:

Dr. Eisenberg: In these animal experiments you mentioned doses on the order of 100 mg/Kg; roughly around 7 grams in the human. How high a dose did you give humans as a medicinal dose to see what effects there were in humans?

Answer:

As far as I am aware, the highest dose given to humans has been 2400 mg per day. Doses ranging to this value have been administered by Dr. Stamps to epileptic patients for periods of 2 years or more without evidence of toxic effects. Even in comparison to this high human dose, however, there is still a several fold discrepancy in mg/Kg dosage between the mouse and human studies. Such a difference is, of course, not unusual in pharmacological studies and two factors probably account for most of it. First, there are usually differences in sensitivity to drugs among species, and second, and perhaps more important, is the fact that in pharmacological studies we are usually concerned with measuring rather marked changes in threshold, or easily recognized drug effects, whereas in humans, clinical effects often result from much more subtle changes requiring relatively low doses.

Question:

Dr. Dorfman: When you studied the long term toxicity, did you include studies of the brain with microscopic sections? In some studies reserpine and chlorpromazine have shown minor changes in the brains of monkeys following chronic administration.

Answer:

No, there was no microscopic study of the brains of chronically treated animals. This was not considered necessary for two reasons. Gross examination of the brains of treated animals yielded no evidence of pathology, and, more important, no clinical signs of irreversible CNS effects were ever observed with hydroxyphenamate.

Effect of Hydroxyphenamate on the Conditional Psychogalvanic Reflex in Man

LEO ALEXANDER, M. D.*

The known differential effects of psychotropic drugs have made it desirable to investigate the objective parameters of these drug effects. For this purpose, we have studied the conditional responses of patients before and after the administration of single doses and also after prolonged drug administration. Observations concerning a number of drugs so studied were reported earlier.[1-5] From combinations of the changes in magnitude of the responses and in the quality of differentiation between the responses to the excitatory and inhibitory signals, profiles emerged which were remarkably characteristic for certain drugs or groups of drugs.[5]

Hydroxyphenamate (Listica®) is a new drug whose target symptom appeared to be impulsive behavior, when administered to patients suffering from psychotic and neurotic states with psycholeptic features; i.e., abnormal mental states in which bewilderment, panic and impulsivity were prominent features, including psychomotor epilepsy. The effect of the drug upon impulsivity appeared to be independent of clinical diagnoses, but depended on whether or not the target symptom "impulsivity" happened to be a key symptom[6] in the patient's disturbance, ranging from the impulsivity of the obsessive-compulsive character with oral sadistic trends who disrupted his family life and came to psychiatric attention primarily as a marital problem, to the ictal and non-ictal behavior of psychomotor epilepsy, and including not only schizophrenics with cataclysmic-psycholeptic experiences, but also less globally disturbed schizophrenics, either paranoid or pseudoneurotic, who were given to impulsive crisis reactions in their interpersonal relations.

The drug reduced tension without being euphoriant, and in the standard dosage administered in our study (200 mg. 3 to 4 times daily) appeared to have less inhibitory effects than a variety of other tranquilizing drugs. This made it possible to administer this drug over sufficiently long periods to a number of patients who used to discontinue other drugs after a short time of trial, with the complaint that they had made them feel "dull", "non-alert", "bored" or "tired", although they were quite effective for the control of their main symptoms. This complaint occurred only very rarely with regard to hydroxyphenamate at our standard dose. A number of patients tolerated also a much larger dose (400 mg. 4 times daily) without such side effects. In all but one of these cases this larger dose was arrived at only after a month long preliminary trial of 200 mg. 4 times daily had proved ineffective in controlling the disturbance. One patient complained of drowsiness on a dose of 400 mg. 4 times daily given initially, but tolerated a dose of 200 mg. 4 times daily without such side effect. Two patients developed arterial hypotension on a dose of 400 mg. 3 to 4 times daily but this was relieved by reduction in dosage or discontinuance.

Case Material:

The present study is based on 22 of 28 patients who were treated with this drug. The total group included 4 patients suffering from obsessive-compulsive states, 2 patients with obsessive-compulsive character neurosis, 2 phobic states, 6 depressive reactions, 1 anxiety reaction, 7 schizophrenic and schizo-affective reactions, 5 patients suffering from psychomotor and related forms of epilepsy, and 1 from a postcraniotomy headache, after removal of a subdural hygroma. One-half of the group achieved complete and/or social recovery under treatment, namely: the 2 patients with obsessive-compulsive character neurosis, 2 obsessive-compulsive states, 1 phobic state, 2 depressive reactions, 4 schizophrenic and schizo-affective reactions, and 3 of the

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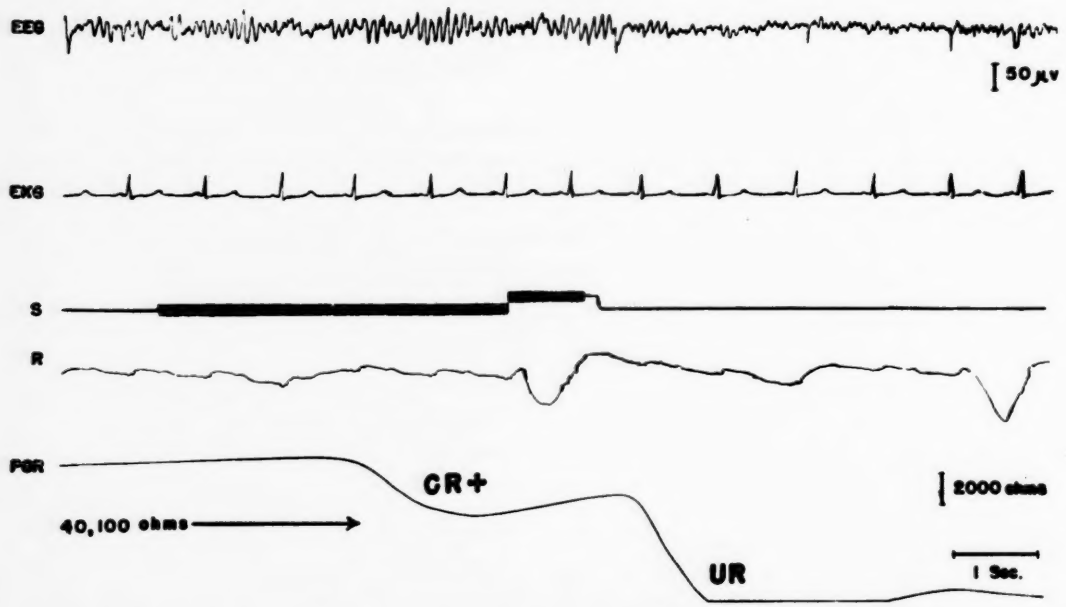

Figure 1 — Female, age 27, suffering from schizoaffective disorder. Polygraphic recording illustrating the psychogalvanic reflex responses to the fourth presentation of the excitatory (reinforced) tone and its overlapping shock stimulus. (EEG = electroencephalogram; EKG = electrocardiogram; S = signals (the thick black line denotes the sounding of the tone, the elevation of the base line of the signal channel denotes the shock stimulus to the index finger); R = respiration; PGR = psychogalvanic reflex.) Note conditional PGR response to the excitatory (reinforced) tone (CR+), consisting of a drop in skin resistance of 4000 ohms beginning 2 seconds after the onset of the tone and unconditional PGR response to shock (UR), measuring 7200 ohms, beginning 1.5 seconds after the onset of the shock.

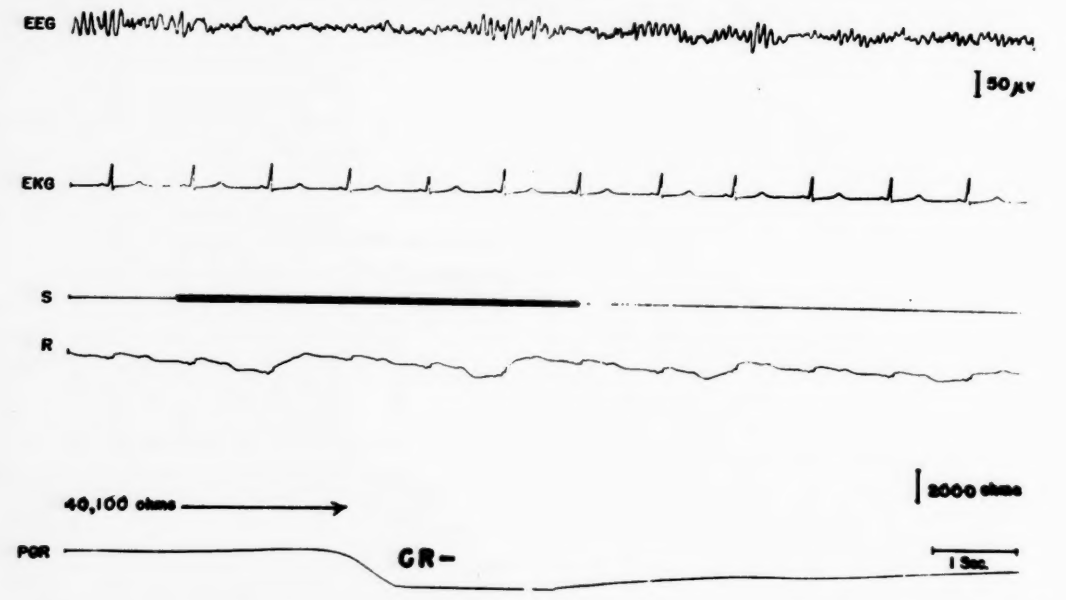

Figure 2 — Female, age 27, suffering from schizoaffective disorder. Polygraphic recording illustrating the psychogalvanic reflex response to the fourth presentation of the inhibitory (non-reinforced) tone (CR—), consisting of a drop in skin resistance of 2000 ohms beginning 2 seconds after the onset of the tone.

psychomotor epileptics. In 2 of the latter the drug was given in addition to other anticonvulsants which had previously been ineffective and which were gradually tapered off except for token dosages.

Eight patients improved short of social recovery. These, in addition to the 6 unimproved patients, comprised the non-recovered group.

Method:

Twenty-two patients were tested before administration of the drug and retested one hour after administration of the first test dose of the drug (200 mg. p. o.); 9 patients were again retested at the time of establishment of a clear-cut treatment result, either success or failure. These times varied from 9 to 325 days, averaging 68 days, the median being 36 days. Five of these 9 patients were treatment successes; 4 were failures. Four patients, two of each category, were again retested one to two times later, while still on the drug, at treatment periods varying from 36 to 202 days.

The technique of the test is quite simple. After the abolition of the orienting responses, a conditional reflex was established, according to the classical Pavlovian method, by pairing one tone (512 cps.) with an electric shock (at tolerance selected by patient, varying from 0.7 to 2.5 milliamperes, averaging 1.5 milliamperes) to the tip of a finger during the fifth second of the sounding of the tone, while another tone (256 cps), which was never so reinforced, was presented in regular alternation with the reinforced tone at one-minute intervals. Stimuli and responses were recorded by means of a modified Grass polygraph, previously described.[1] For the purposes of quantitative comparison only the psychogalvanic responses were utilized because they are easily and accurately measurable, and hence lend themselves readily to quantitative analysis. The well-known inherent difficulties encountered in attempting to analyze the electrocerebral alerting responses by quantitative methods prevented utilization of this portion of our data for this purpose.

Whenever an evoked psychogalvanic reflex response occurred, it was sharply defined and came within about 1.5-2.5 seconds after the beginning of the unconditional, and within 2-3 seconds after the onset of the conditional stimuli. It consisted of an easily distinguishable drop in skin resistance, measured in ohms. Thus, the reaction to the excitatory (reinforced) tone and its overlapping shock stimulus consisted usually of two deflections: the first to the tone, classified as the excitatory or positive conditional response (CR+); the other to the shock, classified as the unconditional response (UR) (Figure 1). The response to the never-reinforced, that is the inhibitory tone, was called the inhibitory conditional response (CR–). In cases of perfect differentiation, such a response was absent and counted as zero. When response to the inhibitory tone occurred, this was usually a response to the one effect; i.e., to the first second of the sounding of the tone, appearing about two seconds after the start of the tone, classified as CR– (Figure 2). This was sometimes followed by an additional response to the fifth second of the tone, occurring about one second after termination of the tone (Figure 3), classified as a generalized time reflex (GTR), since it is obviously a generalization effect by means of a time reflex patterned after the excitatory tone and its overlapping unconditional stimulus.[1,5]

These four psychogalvanic reflex responses were measured as ohms drop in skin resistance for each pair of presentations of the tones for all patients before and after administration of the drug. Averages for the responses in each of these four categories were calculated in ohms for each conditioning session which uniformly consisted of 12 pairs of presentations. The bar graphs included in this paper represent the averages computed for each conditioning session.

Conditionability, or the ability to differentiate between the inhibitory and the excitatory signals, was calculated as the ratio of the average response to CR+ divided by the average response to CR–. Thus the conditionability ratio (briefly termed "ratio" in our tables) was determined for each conditioning session and a rise or fall in ratio after drug administration signified improvement or worsening of the ability to form conditional reflexes.

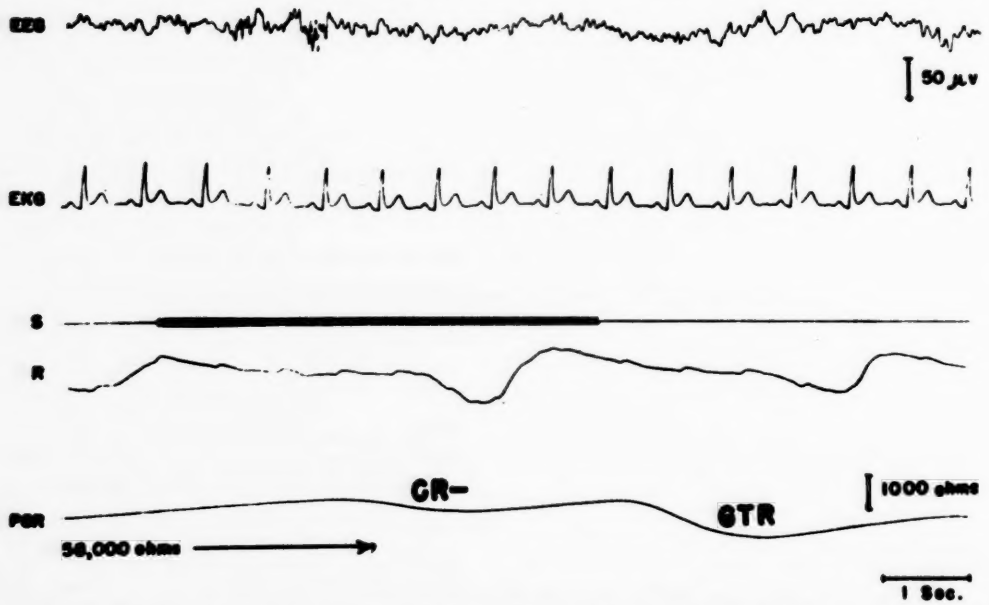

Figure 3 — Male, age 24, suffering from psychoneurosis, phobic reaction with obsessive features. Polygraphic recording illustrating a psychogalvanic reflex response to the inhibitory tone (CR—) occurring 2 seconds after the onset of the tone and an additional psychogalvanic reflex response beginning 0.8 seconds after the end of the tone interpreted as a generalized time reflex (GTR) patterned after the response to the excitatory tone and its reinforcing stimulus (compare Fig. 1).

Results

Initial effects noted included improved differentiation with a tendency toward increased conditional responses to the excitatory stimulus (Figs. 4, 5, 6). This occurred in the majority; namely, 14 of the 22 cases, which was not statistically significant (Table I). Another feature of the acute effect in more than half of the patients was an enhanced response to the unconditional signal, which occurred in 12 of the 22 patients tested (Figs. 5 and 6). When these patients were questioned after the conditioning session they stated that the unconditional signal "felt stronger". According to Astrup, [7,8,9] increased response to the unconditional signal is a significant feature of improvement of psychosis irrespective of how it came about, whether spontaneous or treatment-induced. This was an item of early drug action on the part of this drug which had not been observed by us with any other drug studied.[5] However, this item did not differentiate in our present small series between the patients who subsequently recovered from those who did not.

TABLE I

Hydroxyphenamate

Retest 1-2 hrs. after first test dose (200 mg p.o.)
N = 22

	PGR Responses				
	N down	*N even*	*N up*	X^2	*P*
CR—	12	0	10	0.182	.90
CR+	10	0	12	0.182	.90
Ratio	8	0	14	1.636	.20
UR	10	0	12	0.182	.90
GTR	12	1	9	0.429	.50

The long-range result tested at the time of establishment of the clinical effect following 9 to 325 days of medication at a dose of 200 mg. 3 to 4 times daily (with the inclusion of one patient treated with a dose of 400 mg. 3 times daily), showed a marked reduction of the conditional responses (Figs. 4, 5, 6, 7) without significant change in the differentiation ratio (Table II). This aspect of the long-range effect of hydroxyphenamate was similar to that of the phenothiazines and the amine oxidase inhibitors.

However, the long-range response to hydroxyphenamate shows a significant difference from the effect of the phenothiazines in that hydroxyphenamate did not significantly reduce the unconditional response (Table II; note also the remarkably

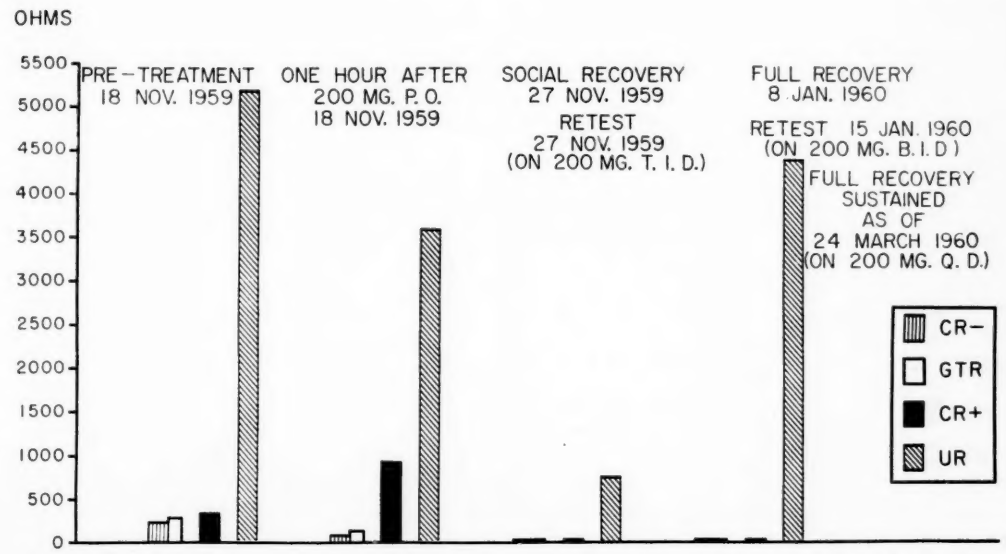

Figure 4 — Female, age 27, schizophrenic reaction, acute paranoid state, with cataclysmic-psycholeptic experiences. Treatment with hydroxyphenamate from 18 November 1959 until 13 October 1960. Note improved differentiation after first test dose. Note also marked reduction of conditional responses at the time of social recovery and at the time of full recovery. Also note increased magnitude of unconditional response when dosage was reduced from 200 mg 3 times daily to 200 mg twice daily.

In this and the subsequent bar graphs, CR− denotes the average conditional psychogalvanic reflex to the inhibitory signal; GTR denotes the average generalized time reflex; CR+ denotes the average conditional psychogalvanic reflex to the excitatory signal; UR denotes the average psychogalvanic response to the unconditional stimulus.

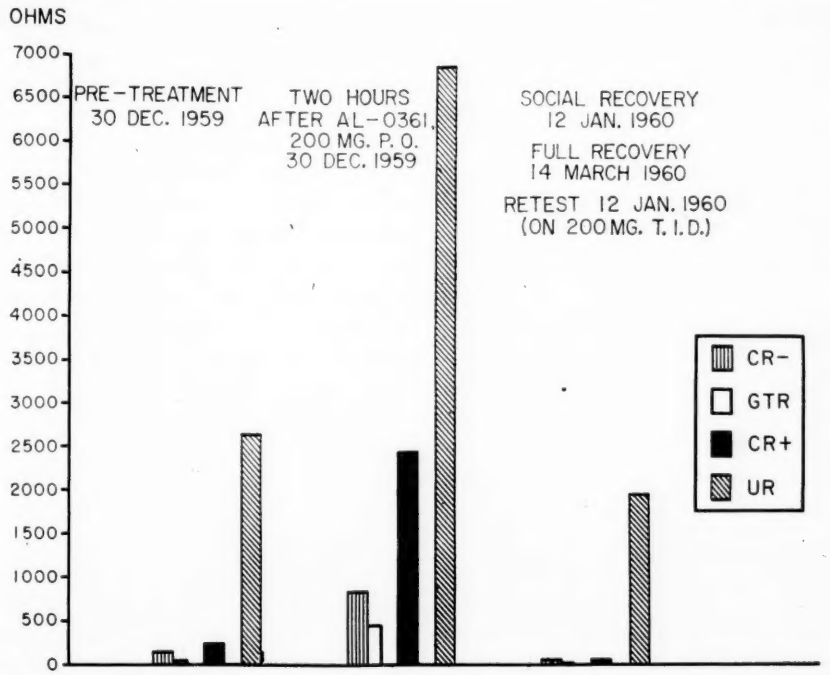

Figure 5 — Female, age 60, depressive reaction, manic-depressive, recurrent, psychotic, pyschasthenic-anhedonic (issue: power-envy). Treatment with hydroxyphenamate from 30 Dec. 1959 to 1 Feb. 1960. Note improved differentiation and enhanced unconditional response two hours after the first test dose. Note reduced responses at time of recovery.

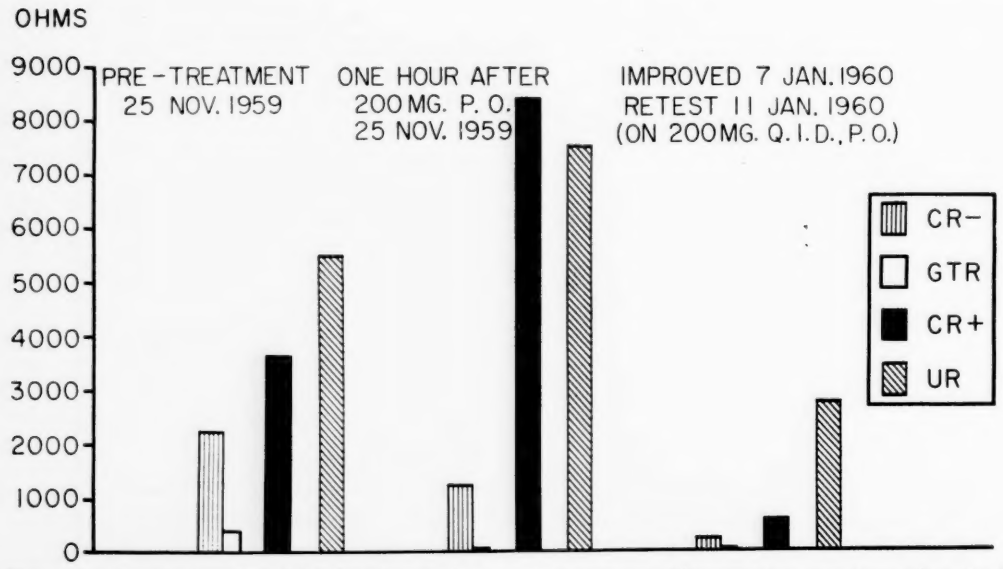

Figure 6 — Female, age 23, schizophrenic reaction, pseudoneurotic, with paranoid and obsessive features and with neurocirculatory somatization reactions. Treatment with hydroxyphenamate from 8 Dec. 1959 to 22 Jan. 1960. Note reduction of the conditional response to the inhibitory signal, and enhanced response to the excitatory signal, resulting in improved differentiation one hour after the first test dose. The response to the unconditional stimulus is increased also at that time. Note greatly reduced responses after 47 days of treatment at time of improvement which, however, remained short of social recovery.

well-preserved unconditional response in Fig. 4), while the phenothiazines reduced the unconditional response at better than the .01 level of significance (Table III).

The long-range response to hydroxyphenamate differed from that of the amine oxidase inhibitors in that hydroxyphenamate reduced the generalized time reflex at better than the .01 level of significance (Table II), while the amine oxidase inhibitors did not (Table IV).

The reduction of the generalized time reflex by hydroxyphenamate may be an objective corollary of its anxiety-reducing effect, while the preservation of the unconditional response may reflect the high state of general alertness exhibited by the patients as well as the absence of a significant adrenergic effect of the drug. The significant reduction in responses to the inhibitory stimuli (at better than the .01 level of significance) and to the excitatory stimuli (at better than the .05 level of significance) in our patients (Table II) appears thus to

TABLE II

Hydroxyphenamate

Mean Treatment Time: 68 (9 = 325) days
(200 mg 3 to 4 times daily, with the inclusion of one patient receiving 400 mg 3 times daily)

N = 9

	PGR Responses				
	N down	*N even*	*N up*	X^2	*P*
CR−	9	0	0	9.00	<.01
CR+	7	1	1	4.50	<.05
Ratio	4	0	5	.11	.75
UR	6	0	3	1.00	.30
GTR	9	0	0	9.00	<.01

TABLE III

Phenothiazines

N = 10

	PGR Responses			
	N down	*N even*	*N up*	*P*
CR−	8	1	1	<.05
CR+	9	1	0	<.01
Ratio	5	1	4	.50
UR	9	1	0	<.01
GTR	6	3	1	.063

TABLE IV

Amine Oxidase Inhibitors

N = 15

	PGR Responses			
	N down	*N even*	*N up*	*P*
CR−	13	0	2	<.01
CR+	13	0	2	<.01
Ratio	9	0	6	.608
UR	11	1	3	.058
GTR	9	2	4	.266

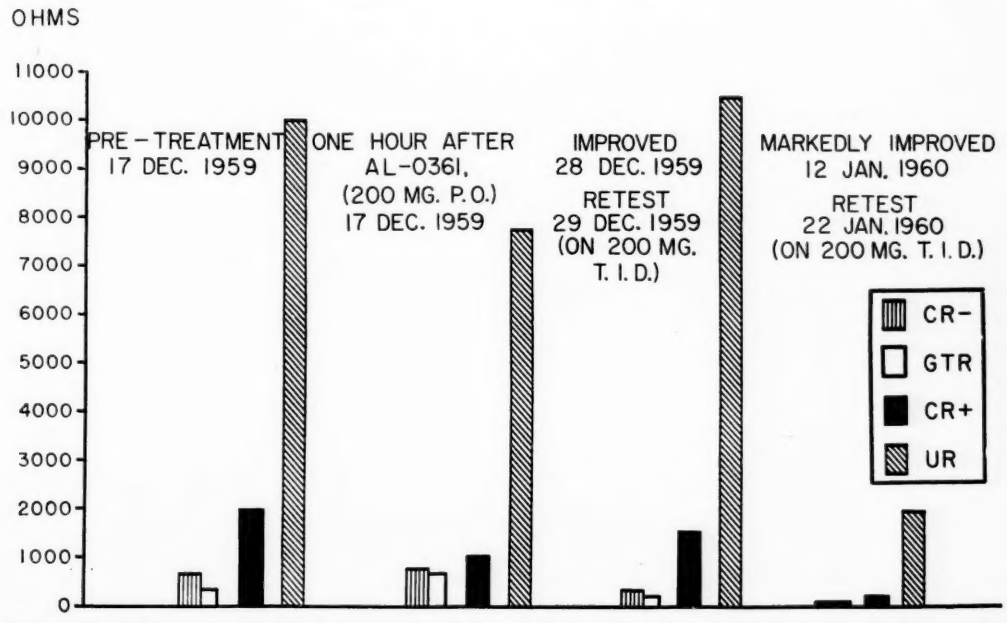

Figure 7 — Male, age 52, psychomotor epilepsy (schizo-affective reaction with psycholeptic features) with frontal and anterior temporal dysrhythmia. Treatment with hydroxyphenamate from 17 Dec. 1959 until the present. Note reduced differentiation between responses to the inhibitory and excitatory signals and reduced unconditional response one hour after first test dose; improved differentiation and slightly enhanced unconditional response after 12 days of treatment, which had resulted in improvement. Note markedly reduced conditional and unconditional responses 25 days later, ten days after manifestation of marked improvement which, however, still remains short of social recovery.

be representative of a reduction in conditional interaction with the environment, indicating a protective drug-induced inhibition, which isolates the individual from stressful conditional stimuli.

The difference in the immediate drug effect from that after prolonged administration suggests a cumulative effect, in the light of the fact that drugs which bring about inhibition of responses at the usual therapeutic dosage level may, at a lower dosage level, produce disinibition of differentiation.[1,2,10] This may explain the fact that the patient whose responses are shown in Figure 7, a man of heavy athletic build, weighing 250 lbs., showed disinhibition of differentiation still after 12 days of treatment, while the marked reduction of responses characteristic of the prolonged drug effect did not come about until 25 days later (Figure 7).

There was no evidence of tolerance. The pattern of change was preserved when the patient was retested a second or third time after the conditional responses had been reduced concomitant with achievement of the treatment result, and while remaining on full or maintenance dosages of the drug for another 24 to 193 days. On maintenance therapy, however, the unconditional response may again increase, while the inhibition of the conditional reflexes remains unaltered (Figure 4).

Summary

Hydroxyphenamate, a drug which influences impulsive - psycholeptic behavior, brings about significant reduction of the conditional psychogalvanic reflexes to the inhibitory and excitatory stimuli, as well as significant reduction of the generalized time reflex. The differentiation ratio and the unconditional psychogalvanic reflex are not significantly altered. This drug response differs from that to the phenothiazines which bring about significant reduction of the unconditional psychogalvanic reflex as well, and differs from that to the amine oxidase inhibitors, which do not significantly affect the generalized time reflex.

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Amelioration of Allergic Symptoms with a New Tranquilizing Drug (Listica)

BEN C. EISENBERG, M. D.*

Many allergic patients, despite vigorous symptomatic and specific therapy, often show a "break-through" of their previous symptomatology, not because of increased insult from physical factors, but due to stressful life situations such as family or work problems, anxiety, guilt feelings, fear, hidden anger and resentment. Previous investigation[1] had found a number of psychotropic drugs helpful in allaying various manifestations of allergic disease where psychogenic factors predominated or interfered with proper immunologic responses to hyposensitization therapy.

A victim of hay fever or asthma may suffer from various neuropsychiatric disorders, and his depression or anxiety state may reach such proportions as to require definitive treatment. The modern allergist, in embracing an "holistic approach" toward his patients and their problems, will treat the individual as a whole – i.e., attempt to control his symptoms, identify etiologic factors, both physical and emotional, and make an appraisal of his effectiveness as an individual and how he reacts to life, family, friends, and fellow-workers.

Concerning the use of psychopharmacological agents, physicians should acquaint themselves with the various classes of these drugs, their mode and site of action, indications for their use, and proper dosage. One need not know the structural formula of every medication prescribed, but a glance at the chemical descriptions or structural formulae will enable one to immediately catagorize a substance. Thus, when a new drug is introduced for the express purpose of modifying mental activity, it is possible to predict not only its therapeutic effect, but some of the adverse reactions as well, just from reviewing its chemical description and configuration. It would then be more difficult for a manufacturer to hide from the observant physician a new phenothiazine derivative, for example, behind some fancy generic term.

Most agents used for psychotherapeutic purposes fall into one of three general types, depending on their major effect. Chart A gives a simplified classification to distinguish a drug according to its clinical response.

CHART A

Classification of Psychotropic Drugs

1. Central Nervous System Depressants:
   a. Hypnotics and Sedatives.—reduce degree of awareness and wakefulness; produce sleep. Examples—barbiturates, morphine.
   b. Ataractics (Tranquilizers).— reduce anxiety, tension, fear; very useful in major psychoses; calms excitable, perturbed patients. Examples – phenothiazines (chlorpromazine, prochlorperazine, perphenazine), reserpines, haloperidol, trifluoperazine, chlordiazepoxides, hydroxyphenamate.
   c. Muscle Relaxants. – anticonvulsant, reduces anxiety and tension states. Examples—meprobamate, chlormezanone, zoxazolamine, mephenesin, methocarbamal, styramate.
2. Central Nervous System Stimulants:
   a. Anti-Hypnotics and Psychotonics.—produce wakefulness, increased awareness; antagonize barbiturates. Example—amphetamines.
   b. Anti-Depressants.—psychic energizers, produce remission in depressed states; blockage of pain transmission (angina pectoris, rheumatoid arthritis, ulcerative colitis). Example—amine-oxidase inhibitors (such as the hydrazides [iproniazid, isocarboxazid, phenelzine, phenipramine, nialamide]), dibenzazepines (imipramine) and deanol.
3. Hallucinatory and Depersonalizing Drugs:
   a. Artificial Psychosis Producing Compounds.—create confusion, hallucinations, distort appreciation of reality values. Useful in research of disturbed mental states, to test efficacy of psychotropic drugs in relieving psychoses. Examples—lysergic acid diethylamide (L.S.D. 25), psilocybine, psilocin (Mexican mushroom), peyote.

Nearly all psychotherapeutic drugs so far produced[2] have complications from their use, some serious. It is therefore commend-

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able that the pharmaceutical industry continues its search for safer and more effective tranquilizers. We are getting increasing reports of marked adverse effects from the preparations now in use. Phenothiazine derivatives have produced profound mental depression in some patients, delusions, hallucinations, toxic psychoses, catatonia, parkinsonism, akathisia, and dystonia, even major convulsive seizures. Other toxic results from this group include: allergic reactions (dermatitis, serum-sickness type of response, purpura), blood dyscrasias, jaundice, gynecomastia in men, menstrual irregularity and lactation in women, severe (sometimes fatal) hypotension, paralytic ileus and bladder paralysis. Also, pronounced withdrawal symptoms may ensue when phenothiazines are stopped too suddenly.

Meprobamate (Miltown, Equanil) dots our literature occasionally with additional reports of serious side reactions. Besides severe, generalized skin eruptions, anaphylactoid reactions have been recorded, also chills, fever, stomatitis, proctitis, aplastic anemia, erythema multiforme, and muscular rigidity. This tranquilizing agent is likely to cause addiction after prolonged use in excess of 800 mg. per day and also serious withdrawal symptoms.

Even the more recent additions to the field of psychopharmacology, the monoamine oxidase inhibitors, have produced adverse reactions in patients. These compounds often produce profound central nervous system effects of an undesirable nature such as inhibition of sympathetic activity, constipation, postural hypotension, and urinary retention. It must be kept in mind that some of these amine-oxidase inhibitors potentiate the pharmacologic action of several unrelated drugs, i.e., chlorothiazide, atropine derivatives, opiates, sedatives, corticosteroids, ganglionic blocking agents and some of the quinoline group of anti-rheumatic drugs. Besides, the amino-oxidase compounds are effective in only about 1/3 of the endogenous depression cases. Toxic manifestations include normocytic-normochromic anemia (incidence 6%), skin eruptions (1%), jaundice from hepatocellular damage, agranulocytosis, and red-green color blindness (phenipramine).

Rauwolfia alkaloids have been largely replaced by the phenothiazine derivatives for the treatment of major psychoses, although the former still hold a prominent place among the most used hypertensive agents. Reserpine and related substances cause profound mental depression in as much as 26% of cases treated, and there have been a number of suicides reported during the administration of this class of drugs. They produce extrapyramidal effects similar to the phenothiazines, even seizures. Other toxic manifestations include vomiting, diarrhea, bradycardia, excessive salivation, purpura, severe nasal congestion, reactivation of peptic ulcer with hematemesis and melena, edema, feminization of males, and aggravation of allergies such as asthma, pollen hay fever and urticaria.

Recently a new carbamate compound, hydroxyphenamate (T.N.-Listica) was made available for investigation as a calmative or tranquilizing agent for use in allergic patients requiring this type of medication. Pharmacological studies indicate that Listica has many properties similar to phenobarbital, with one-third of the latter's toxicity. The drug is approximately 50% more potent than Mephenesin, and thus far produced no demonstrable toxic effect on hemoglobin, red or white blood cells, the liver, heart, or other organs. Initial investigations by Bastian[3] showed that this new compound is a safe, long-acting central nervous system depressant, and anticonvulsant, especially indicated in anxiety, apprehension, phobias, tension states, psychomotor epilepsy, hyperactivity and behavior problems.

Materials and Method

Listica was administered to patients suffering from various allergic disorders complicated by psychogenically induced states such as anxiety, fear, tension, or mental depression. No control or double-blind studies were attempted at this time. Most of the patients included in the group failed to show adequate improvement from conventional allergic management, while others were selected because of complaints of being emotionally upset, worried, or "nervous". Adult patients were given 200 mg. of the active drug three times daily for

two to six weeks. Children over six years of age took the same amount with the two-to-six age group getting one-half this dose, namely, 100 mg. three times a day. These dosages were doubled in some instances for enhanced clinical effect. The majority of the children included in the study presented either behavior problems or somatic manifestations of emotional illness such as frequent headaches, abdominal distress, night terrors, etc. Table I shows the types of cases treated with Listica. All patients were continued on their regular, conventional, multi-visit hyposensitization program with aqueous antigenic extracts directed against their specific inhalant allergies. Some individuals also continued to take previously prescribed medication, i.e., antihistamines or bronchodilators, as required, but the vast majority took no other medication while on Listica.

TABLE I

Allergic Diagnoses Treated With Listica

	No. Patients
Rhinitis	22
Asthma	6
Both	25
Dermatoses	17
Cephalalgia	10
Male	26
Female	54

As shown in the above table, 26 of the patients under observation were males, 54 females. Ages ranged from 2 to 76 years. Most of the major allergic conditions were represented, as indicated, with respiratory allergies predominating. The emotional complaints listed are those common to any segment of the human population. Children included in this group presented behavior problems (i.e., unmanageable deportment, refusal to go to school) which failed to respond to either psychotherapy or drugs like phenobarbital, chlorpromazine or deanol.

Results

Clinical response to treatment with Listica in 80 allergic patients is summarized in Table II; 43 or 54% showed good to excellent response with respect to relief of nervousness, tensions, etc. In many instances where this benefit was obtained, there was definite amelioration of allergic symptoms, i.e., less headache, rhinitis, itching or wheezing attacks.

TABLE II

Clinical Response with Listica Treatment of Emotional Illness

	No. Patients	
Excellent	24	(30%)
Good	19	(24%)
Fair	18	(22%)
None	19	(24%)

Side effects reported by this group are shown in Table III. Twelve patients complained of adverse reactions, including drowsiness (3 patients), dizziness (3 patients), heartburn or gastrointestinal upset (4 patients), and urticaria (2 patients). One of the latter complained of slight increase in "nervousness" while on the new tranquilizer. All these untoward effects were of mild degree, with the exception of one individual who developed moderate nausea and vomited slightly after a few days of medication. It should be noted that all four cases reporting gastric complaints suffered from recurrent or chronic gastritis or gave histories of past treatment for peptic ulcer. No patient complained of inability to concentrate, and none showed signs of addiction. There was no complaint of increased nervousness, insomnia, restlessness or gastrointestinal symptoms when the drug was stopped.

TABLE III

Side Effects Encountered with Listica in the Treatment of Emotional Illness

	No. Patients
Drowsiness	3
Dizziness	3
Urticaria	2
G-I Upset	4
Total	12
%	15

Discussion

Most of the adult patients treated in this study had tried, and were quite familiar with the effects of other tranquilizing agents such as various representatives of the phenothiazine group, meprobamate, barbiturates, etc. The degree of benefit derived from Listica was determined from reports by the patients. Amazingly, a large proportion of allergic individuals can accurately

assess the impact of psychogenic factors upon their illnesses, once they develop insight into their problems. Based on their statements, 54% reported good to excellent results from the drug under investigation, in that feelings of anxiety, tension, apprehension and other emotional conditions were abated or ameliorated. Quite often, the manifestations of allergy decreased in intensity at the same time.

Obviously, it is most difficult to appraise the effectiveness of drugs in allergic diseases, for conditions to which the patients are subjected vary from day to day, as do the emotional clime and the immune body responses to noxious substances. Even controlled studies employing a double-blind technique, while desirable, will not obviate errors inherent in experiments dealing with such conditions as asthma, chronic rhinitis, and allergic dermatoses – all of which may be subject to change, even within the hour, from so-called, as yet unidentified "X-factors". This brings to mind a recent dramatic case. A 52 year old woman hospitalized with severe status asthmaticus, upon learning that her husband had suffered a heart attack, abandoned her oxygen tent, demanded her clothes, signed herself out and rushed to his side, all signs of wheezing dyspnea gone. This patient had previously responded to no medication whatsoever, including tranquilizers. Even Listica would probably have been of no avail. What was the mechanism by which this cure was so rapidly effected? For the present the question is unanswerable.

Concerning incidence of side effects in the present study, if we exclude the four complaints of gastrointestinal upset, on the basis noted above, that these subjects frequently encountered such difficulties even when off all medication from chronic gastric disorders, the rate becomes reduced to 10%. Complaints about the medication were of a mild order, mostly drowsiness. One case of hives occurred, but this patient had been subject to occasional attacks of urticaria all her life from several foods, as well as from emotional upset. From the present study, there is little real evidence to exclude the drug from our armamentarium on the basis of adverse effects resulting from its use. No patient showed anaphylactoid reaction or any disturbance of the blood, kidneys, thyroid, heart, or liver, as a result of Listica administration.

Summary

Tranquilizing agents are often desirable for their calming influence in those allergic patients who tend to suffer from aggravation of symptoms because of anxiety, tension, apprehension or depressed states. Listica, a new psychotropic drug, found by experimentation to be devoid of toxicity, was administered to 80 patients suffering from various allergic disorders aggravated by emotional conditions; 43 patients (54%) reported good to excellent result, with lessening in the intensity of allergic symptoms in numerous instances. An additional 18 patients (22%) had fair response. Adverse effects were of minor degree, occurring in 12 of the 80 patients. No disturbance of the blood or other organs was noted. This medication did not interfere with specific allergic treatment and was in no way incompatable with other drugs required by the patients.

Author's note: Listica (hydroxyphenamate) used in this study was supplied by Armour Pharmaceutical Company.

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DISCUSSION OF DR. EISENBERG'S PAPER

S. J. TAUB, M.D.

I was very interested in Dr. Eisenberg's excellent paper. We are in complete accord. The question comes up as to the relationship between anxiety states, extreme nervousness, etc., and the allergic diseases. I feel the same way that he does, that this is a contributory thing and not primarily etiologically related at all.

There are a few things that I would like to point out. In asthma, for example, sedation ranks high in the procedures for, and in the treatment of status asthmaticus. Sometimes the family as well as the patient must be sedated. Because of all these

psychosomatic relationships in allergic disease states, it was perfectly natural for the allergist to become intrigued with the role of tranquilization in the treatment of allegic patients. The most important thing for the allergist is to determine the etiology of these allergic states by skin testing. There are certain drugs and tranquilizers like the hydroxyzine group (Atarax and Ataraxoid) which are known to inhibit the antigen-antibody reaction on the skin. We depend on this reaction for our diagnosis, and if these drugs are given there may be no skin reactions whatsoever. Of course, the etiologic diagnosis will then be in doubt. For this reason these drugs are contraindicated.

I have found that hydroxyphenamate has no effect on the antigen-antibody response of the patient nor does it inhibit a skin test. This is determined by the production of the histamine wheal in the patient. After giving the drug we determine how small it is, or if there is any relationship to the size of the wheal, has it been reduced?

With hydroxyzine, for example, I have found that the histamine wheal will be diminished by ½ to ⅓, sometimes completely. So we can not use these drugs and test these patients. This drug, hydroxyphenamate, does not do this in any way. I am particularly intrigued with this drug in its role in asthma. I have found some of the best relief from its use in asthma, and I feel it has no antihistaminic, antiserotonic, antiacetylcholine properties. How does it work? I feel that there is another mediator involved in the production of bronchial asthma. The allergists have not heard too much about it as yet; we call it the slow reacting substance, SRS. We expect great things in that direction. We feel this slow reacting substance is released from the lung in anaphylaxis in man and in guinea pigs. And it has been demonstrated to produce contraction of human bronchial preparations *in vitro*. I am starting work on this phase of the use of hydroxyphenamate with the slow reacting substance because I think this is the field in which it may be of great use.

Effect of Hydroxyphenamate* in the Treatment of Mild and Moderate Anxiety States

(A Double Blind Study with Crossover Pattern)

BURTON CAHN, M. D.†

Since the introduction of chlorpromazine in 1953, no less than 70 tranquilizing agents have been advocated as useful in the treatment of emotional disorders. As of March 15, 1960, a list prepared by the Psychopharmacology Service Center of the National Institute of Mental Health reported 39 psychopharmacological agents available in the United States. This list did not include sedatives and combinations of drugs which were also available. With this maze of tranquilizers, each with its individual indication, dose, side effects and complications, it is small wonder that the choice of a tranquilizer for a given patient must be confusing to the non-psychiatrist. However, the situation need not be as confusing as it appears.

Based on clinical experience of the past five years, this investigator has found it efficacious to divide the tranquilizers into two broad categories. In the first category are those ataractics which are useful in the treatment of the psychotic patient. These compounds are related clinically by the presence in the molecule of the phenothiazine nucleus. Thus, Thorazine, Stelazine, Vesprin, Mellaril, etc. would not be considered the drugs of choice to be used initially in the office treatment of the patient with a neurotic or psychophysiologic disorder. In the second category are those tranquilizing medications which are important in the treatment of mild and moderate anxiety and tension states. These compounds are not necessarily related chemically; and though to date a large number have been introduced, only meprobamate and chlordiazepoxide have found general acceptance. It is in this latter group, i.e., those tranquilizers that one should consider first for the office treatment of neurotic and psychophysiologic disorders, that hydroxyphenamate is included. This study was undertaken to compare the effectiveness of hydroxyphenamate with placebo in the management of mild and moderate anxiety and tension states.

Method

Fifty subjects presenting overt symptoms of anxiety, such as sleeplessness, tremulousness, restlessness, palpitations, excessive sweating, psychogenic nausea indigestion and/or pressure of speech, were selected for study. All were male, in ages varying from 20 to 52 years. All were inmates in a maximum security institution and had been referred for psychiatric evaluation either by the medical examiner or by one of the personnel supervising the inmates after admission.

Institution regulations assured essentially the same daily routine in each subject throughout the study. Each was interviewed individually in order to determine the nature of his illness and the manifestations of anxiety. Specific diagnoses included anxiety reaction in 44 cases, conversion reaction in one case, schizoid personality in two cases, paranoid personality in two cases, and inadequate personality in one case. Prior to administration of medication, the patients were divided into two equal groups of 25 men each, designated as Groups I and II. Subjects received medication four times daily, at the same time each day, for a period of two months. During the first month Group I received medication "A" and Group II medication "B". During the second month the medications were reversed without the subjects' being aware that they were receiving a different drug. Subjects were observed daily at the time of administration of the medication, and each was subjected to a psychiatric evaluation weekly throughout the study.

*Hydroxyphenamate supplied by the Armour Pharmaceutical Company, Kankakee, Illinois, under their tradename Listica.

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At the interviews, nonspecific questions were asked with special care taken to avoid suggestion so that the effect of hydroxyphenamate alone would be evaluated.

The Medication:

Hydroxyphenamate and placebo were administered orally in each case as tablets, identical in size and appearance. Each tablet of hydroxyphenamate contained 200 mg. of the drug, and the placebo contained no active medication. Except for designations "A" and "B", no identifying marks were used to distinguish one tablet from another. Throughout the study neither the subjects nor the investigator knew that "A" was hydroxyphenamate and "B", placebo.

Results

A. Twenty-five subjects were treated initially with hydroxyphenamate for one month; all these subjects receiving hydroxyphenamate initially improved. In eight subjects the improvement was considered excellent; in 14 subjects, good; in three subjects, fair. Side reactions were encountered by four subjects. They experienced drowsiness which, however, did not interfere with their usual routines. The drowsiness generally followed the evening meal but was not of sufficient intensity to compel sleep.

TABLE I

25 Subjects Started on Hydroxyphenamate

Improvement				
Excellent	*Good*	*Fair*	*Poor*	*Side Reactions*
8	14	3	0	4

Total Improved: 25
Total Not Improved: 0

B. Twenty-five subjects changed at the end of one month from hydroxyphenamate to placebo. Only one subject who improved initially on hydroxyphenamate maintained the same degree of improvement when switched to placebo; 24 of the 25 subjects who initially improved on hydroxyphenamate suffered a return of their original symptoms when changed to placebo.

TABLE II

25 Subjects Changed to Placebo

Compared to Hydroxyphenamate:
One subject maintained improvement.
Twenty-four subjects became worse.

C. Twenty-five subjects were treated for one month with placebo. Nine subjects who received placebo initially improved. In three subjects the improvement was considered good; in six subjects, fair; 16 subjects receiving placebo initially underwent no change or showed an increase in the severity of symptoms. No subject who received placebo initially experienced any side reaction.

TABLE III

25 Subjects Started on Placebo

Improvement				
Excellent	*Good*	*Fair*	*Poor*	*Side Reactions*
0	3	6	16	0

Total Improved: 9
Total Not Improved: 16

D. Twenty-five subjects changed to hydroxyphenamate. Twenty-four subjects improved when changed from placebo to hydroxyphenamate. In 10 the improvement was considered excellent; in 13, good; in one, fair. Only one subject failed to improve when changed from placebo to hydroxyphenamate.

TABLE IV

25 Subjects Changed to Hydroxyphenamate Compared to Placebo

Improvement				
Excellent	*Good*	*Fair*	*Poor**	*Side Reactions*
10	13	1	1	4

Total Improved: 24
*Same as Placebo: 1

E. Combined Results. Of 50 patients treated with hydroxyphenamate, 49 improved. In 18 the improvement was excellent; in 18, good; and in four, only fair. Of 50 patients treated with placebo, nine improved; in three the improvement was considered good, in six, fair. Eight subjects, all receiving hydroxyphenamate, experienced mild drowsiness. No other side reactions were encountered. Out of 50 subjects, 47 preferred hydroxyphenamate.

Conclusions

A. Hydroxyphenamate is a compound possessing definite tranquilizing activity in the treatment of anxiety.

B. Its range of activity appears similar to that of meprobamate and chlordiazepoxide, rather than that of the phenothia-

zines and other compounds used to treat the psychoses.

C. Hydroxyphenamate is apparently free of severe or discomforting side reactions. The only side reaction encountered in this study was mild drowsiness.

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DISCUSSION OF DR. BURTON CAHN'S PAPER

Moderator: Dr. Stamps, would you start the discussion of Dr. Burton Cahn's paper?

Dr. Stamps: My patients are all epileptics and most of them have anxieties and the majority are psychomotor epileptics. These patients have severe personality disturbances many far beyond just an anxiety. We have used Listica now for about three years and we were hoping, when we found out that it didn't have much anticonvulsant action, that its tranquilizing effect would cut down on the number of seizures. This was not so. However, I still have a large number of my disturbed patients taking Listica for its tranquilizing effect.

Question:

Moderator: The question I would like to bring up is the criteria which Dr. Cahn had used for improvement. I want him to pin this down because of the many confusions when you talk about improvement in anxiety patients. Would you discuss this?

Answer:

Dr. Burton Cahn: Unlike the allergist, the dermatologist, and other such practitioners, the psychiatrist doesn't have what is considered an objective means of evaluating improvement. The method that I use is as objective as we can possibly make it and it goes as follows: During the psychiatric interview in which I use myself as a sounding board I speak with each individual subject and determine for myself if he looks improved or not, if his psychomotor activity is reduced to a degree where he is not trembling, where he is not fidgeting, where he can sit still long enough to talk with me. This is one objective means. The second objective means I have is that the men in whom I tried hydroxyphenamate were all under 24 hours per day observation. This system is set up so that I can receive reports on their work output, on how well these men are doing in their interpersonal relations with other men, on whether they appear calmer to the people around them, whether they are sleeping better, and so on.

The subjective way I have of evaluating is to listen to the content of what the man tells me in an interview. When a man tells me, "I feel great, I have never felt better in my life, I think this is wonderful, I will gladly pay you for this medicine", then I feel this is excellent improvement. Of course I never accept the pay. I compare this with our objective responses to balance this and make sure that what he is feeling is actually in accord with his behavior. The moderate degree of improvement is again based on the subjective and the objective comparison. If the subject tells me, "Well I feel pretty good, I become anxious occasionally but not nearly as anxious as I was feeling. I can now work, I can now sleep", and this is borne out by the objective response, I call this moderate improvement. Minimum improvement I consider when the man can sleep a little better and this is borne out objectively, and there is no other improvement made. No improvement is, of course, where there is no change.

Use of Hydroxyphenamate in Some Forms of Cardiovascular Disease

EDWARD B. GREENSPAN, M. D.*

During a study of the results of hydroxyphenamate (Listica) in a large group of patients requiring tranquilizers, a small segment of cases with cardiovascular disease were reviewed and herein presented. The group selected had coronary arteriosclerosis with angina pectoris, essential hypertension and chronic cardiovascular disease due to antecedent rheumatic fever.

The drug treatment of angina pectoris due to coronary artery disease has changed but little in the past 100 years. Guthrie first used amyl nitrate in the treatment of angina pectoris in 1867; his treatment was predicated on a wrong premise — that the attack of angina was due to a paroxysm of hypertension, and not as is known now, that it is due to an ischemia of the myocardium. Other forms of nitrates have been used in this therapy, the most popular being nitroglycerin which is glyceryl trinitrate. The value of nitrates is predicated on the fact that the nitrate ion (NO_2) is liberated in the body and is responsible for the vascular dilatation.

During the past two decades, various sedatives have been added to the therapeutic armamentarium for their effect in the handling of patients with angina pectoris. The barbiturates, particularly phenobarbital, the bromides, and chloral hydrate were given to allay the anxiety and relieve the tension that often plague the patient with coronary artery disease and angina pectoris, and essential hypertension. More recently, the use of sedatives has gradually been supplanted by the use of tranquilizers.

The present study was of twelve cases of coronary artery disease and angina pectoris, eight cases of arterial hypertension and three cases of chronic rheumatic cardiovalvular disease with mitral stenosis and insufficiency. The twelve cases of coronary artery disease who had to use nitroglycerin to allay their pain were treated with Listica, a tranquilizer. Observations were made over a two week period, and the number of nitroglycerin tablets used daily was tabulated for comparison with a similar two week period when Listica, 200 mg., three times a day, was added to the treatment. The eight cases of arterial hypertension and the three cases of chronic rheumatic heart disease were given Listica also. Listica is a 2 phenyl— 2-ethyl, 2- hydroxyethyl carbonate.

TABLE I

Summary of Cases Taking Listica

Case No.	*Name*	*Sex*	*Age*	*No. of Coronary Artery Attacks*	*Use of nitroglycerin tablets daily for attacks of angina pectoris*	
					Before Listica	*After Listica*
1	T. K.	M	68	1	1-5	0-1
2	E. S.	F	62	1	2-3	0-2
3	R. J.	F	70	2	1-2	0
4	B. J.	M	66	1	5-8	3-5
5	W. C.	M	55	1	0-2	0-1
6	A. K.	F	54	1	2-5	0-1
7	A. G.	M	55	1	0-3	0-2
8	E. T.	M	62	1	0-5	0-2
9	R. M.	M	59	1	0-3	0-1
10	B. G.	M	60	1	0-5	0-2
11	C. W.	M	66	1	1-2	0-1
12	S. S.	M	69	2	0-4	0

Studies with Listica reveal an absence of toxic findings in the hemoglobin, red blood cells, white blood cells and differential counts done before, and at weekly intervals, in rats, cats and rabbits treated with this drug. There have been no known contraindications to the use of Listica except for the usual precautions in prescribing drugs.

While these results are interesting and appear conclusive, one must be cautious in evaluating the treatment of attacks of angina pectoris. We know the effect of the power of suggestion or placebos in preventing an attack in this type of case.

All eight cases of essential hypertension were under treatment with rauwolfia derivatives and chlorothiozide for various lengths

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of time — the shortest period was two weeks; the longest, three and one-half years — before Listica was administered. While there was no appreciable decrease in dosage of antihypertensive drugs administered, these hypertensive cases felt more relaxed. In one patient with a very labile hypertension, whose elevated blood pressure could be traced to work tension, Listica was very helpful in maintaining a lowered blood pressure to within normal limits.

In the three cases of chronic cardiovalvular disease due to rheumatic fever, there was an appreciable subjective feeling of relaxation and one patient stated that she was less aware of her heart beat. (This patient was known to have frequent periods of premature ventricular contractions and was unable to take quinidine sulfate.

Summary

Twelve cases of angina pectoris in patients who had coronary artery thrombosis were studied. Statistically, the results indicate a decrease in the daily use of nitroglycerin when Listica was administered.

Among the eight cases of essential hypertension and in the three cases of chronic valvular disease due to rheumatic fever, Listica proved to be helpful in maintaining a relaxed, less tense state.

DISCUSSION OF DR. GREENSPAN'S PAPER

Question:

Dr. Dorfman: I think Dr. Greenspan has made a point in indicating that a placebo effect and a suggestive effect can act to decrease the number of angina attacks. This, I think, is very pertinent. It is important to correlate the point of view of the psychiatrist with that of the non-psychiatrist so that they understand each other. The goal of the cardiologist is quite different from that of the psychiatrist. So, when Dr. Greenspan says less tension and more relaxation, as a former internist I agree with him. As a recently converted psychiatrist I must ask how much relaxation and how long it is it going to last?

Moderator: I am glad that question came up. As a psychiatrist I also had the feeling that I didn't know exactly what the objective of the internist was in this case. I wonder if you could make a few comments on this, Dr. Greenspan.

Answer:

Dr. Greenspan: I specifically mentioned the one case of a man who is now in his early fifties whom I have followed for at least 20 years. He had a very labile hypertension. He was in a business which required a great deal of pressure work, and during the periods when the pressure was great he always came in with 180 to 190 systolic pressure and a diastolic pressure of over 100-110. With the use of Listica the results were excellent. For at least seven weeks during the height of his season, for the first time since I have known him, his blood pressure remained normal. It remained around 140/90-92 which I consider a normal level for him.

Now what I meant by relaxation is that the patients would tell me that they didn't have tension headaches; they weren't irritable; they were able to do their work, their house work or whatever work they did, in a more affable manner. I felt that that was the cardiological objective. Now, from the psychiatric point of view I think one must delve deeper into a sense of relaxation where one is thinking of many other factors, including integration of the person and all that.

Question:

Moderator: Do you feel that those are the important factors that are necessary for the cardiologist?

Answer:

Dr. Greenspan: Yes, I think those are the important factors; when the patient feels subjectively better he is not as prone to have attacks of angina pectoris.

Question:

Dr. Rhoades: How frequently did you see the patient during those seven weeks that he improved?

Answer:

Dr. Greenspan: I saw him at least three times a week; he happens to be a personal friend and I wanted to follow him very closely; sometimes four times a week.

Question:

Dr. Rhoades: How often did you motivate him by telling him how effective the drug was?

Answer:

Dr. Greenspan: I didn't mention that at all. I didn't discuss the drug at all with him. I just said, "I want you to take this new drug and see how it affects you." I have tried other things on him in the past and they have not helped.

Question:

Dr. Lunde: Were there any electrocardiographic changes?

Answer:

Dr. Greenspan: Yes, there are electrocardiographic changes in the premature ventricular contractions. Distinctly diminished.

Question:

From the floor: How about your angina patients?

Answer:

Dr. Greenspan: Yes, all these cases of angina

pectoris, as I stated earlier, had a history of a previous coronary thrombosis as I showed in the slide. Some of them had two attacks of coronary infarction. Every case that was shown in the angina group had a previous history of coronary thrombosis.

Question:

Dr. Dorfman: Were there changes in the electrocardiogram?

Answer:

Dr. Greenspan: No, there were no changes in the electrocardiogram that were influenced by Listica.

Question:

Dr. Alexander: How does it compare with the effect of the amine oxidase inhibitors?

Answer:

Dr. Greenspan: I have tried Librium, I have tried nialamide and Tofranil. I don't find good results with people above 55 and 60. I don't find the monoamine oxidases help me as much as a tranquilizer of this type.

Question:

Dr. Taub: We know that angina pectoris is a suggestive symptom. I think it would be very interesting for Dr. Greenspan to do a double blind study on these angina patients.

Answer:

Dr. Greenspan: That has been answered many times. I am at Mt. Sinai where Dr. Master and his group have done a considerable amount of work with various agents in the treatment of angina pectoris over the years. I have been there for over 25 years now, and I know this work well. They have used glucose and other tablets and that is why I made the statement that one has to be very cautious in evaluating the effect of drugs on the treatment of angina pectoris. A double blind study would give us some indication, but again, a double blind study would not be any more efficacious than any other method because these people do sometimes respond, even with the power of suggestion.

Dr. Alexander: I wanted to suggest to Dr. Greenspan a method for diagnosing physical pain. You can differentiate by means of the psychogalvanic reflex between physical and psychogenic pain states. I am going to read a paper containing this suggestion at the International Psychiatric Congress in Montreal. I mention that in the physical pain cases you have a spontaneous fluctuation of the PGR that is greater than both conditioned responses. That difference is significant at the 0.01 level. I recently had a case that shows the limitations of ordinary clinical examination. A very depressed lady came to me, complaining, among other things, of an excruciating pain in her chest. She didn't give much of a history and I assumed this was part of the psychiatric depressive syndrome. However, when the conditioned responses were analyzed she showed a very peculiar pattern. She showed a general depression of responses characteristic of depression but she showed extraordinary spontaneous fluctuations. So, I put her on my work sheet and said here is one case that will throw the chi squares the other way, a psychiatric state with spontaneous fluctuation, but thought that sooner or later I'll have one. Meanwhile I called up the doctor who referred her and said that she was quite depressed, but she also had an indication of physical pain. He said, "Oh you mean angina pectoris. I've been treating her for angina pectoris for years." The lady didn't tell me that as she gave a rather poor history and the doctor had forgotten to warn me but I picked it up from the conditioned responses. Incidentally her angina pain was greatly relieved by Tofranil along with the depression.

Dr. Greenspan: I am sure all of the people in internal medicine who see a lot of cardiology are faced with the problem many times of having a patient come in with a pain in the chest radiating down the arm, sometimes localized in the chest alone. The electrocardiogram shows no changes even after the exercise tolerance test which we do in all these cases. Some of us have had cases with a negative electrocardiogram and who showed no history of angina. These cases subsequently had a coronary thrombosis with a myocardial infarction. Now I have learned from bitter experience to take these patients seriously. Even though at first seeing them you may suspect that this is just a malingering or subjective emotional symptom which is not real. Yet, I have had the experience of patients with angina pectoris with normal electrocardiograms and normal exercise tolerance tests which subsequently came down with a coronary artery thrombosis. So, one must always give the patient the benefit of the doubt. And I think your test might be of value in this type of case.

Pharmacological Approach to the Treatment of Headache

ARNOLD P. FRIEDMAN, M. D.*

The substantial progress made in pharmacological research and in our knowledge of the basic mechanisms of head pain has led to optimistic hope that a new era in treatment of headache by chemical agents has begun. A critical review of the literature would indicate that the tenfold increase in the number of remedies for treatment of headache bears no relationship to their effectiveness. When one considers that in migraine over 400 remedies have been suggested for treatment of this disorder, it is unlikely that our treatment is wholly effective.

The selection of suitable therapy depends on correct diagnosis, which requires the physician to have a basic knowledge of the underlying physiological and psychological mechanisms associated with headache.

My purpose in this paper is to consider some basic principles in clinical appraisal of drugs used in the treatment of headache and to evaluate some of the drugs used in the treatment of muscle tension headache.

Criteria and Basic Principles

In approaching the treatment of headache by pharmacological methods, we are confronted with a number of factors which are difficult to control in the evaluation of our results. They are: (1) Headache as a symptom is a subjective response, and evident only to the individual experiencing it. The appraisal of therapy depends upon a cooperative statement made by the subject experiencing the discomfort. (2) When giving a drug for headache, we are evaluating the original sensation of pain, as well as the reaction to pain. (3) Response to a remedy will be mitigated by the patient-physician relationship, constitutional make-up, and the age of the patient, psychological status of the patient, and the physician's understanding of the pharmacologic action of the drugs being used. (4) The production of model or induced headaches in patients and appraisement of the results of chemical agents are not as reliable as treatment of spontaneous headache.

In spite of these deterring factors, evaluation of results of treatment with drugs in patients with headache can be made.[1] The following general principles and practices are suggested:

Evaluation of both symptomatic and prophylactic therapeutic agents for headache requires the comparison of groups of patients randomly assigned to the treatment under investigation. Double-blind techniques and the inclusion of a placebo, standard drug of reference for comparison, standardization of order, correlated data, mathematical validation of differences, and the appraisal of side effects, are essential parts of any pharmacological study with headache patients. In all studies, discrimination among drugs for the relief of pain can be made only by subjects who have pain on which the chemical action can be tested.

Effectiveness of the agent may be measured in terms of difference in frequency, severity, and duration of attacks, observed among groups over a period of one to two years.

Probably the greatest source of error in reporting results of headache therapy is lack of established criteria for diagnosis, pending the development of relevant objective diagnostic criteria, characteristic patterns of clinical manifestations furnish the only practical basis for classification and hence uniform treatment of headache. Establishing specific diagnostic criteria for the various types of chronic recurring headache would insure that each investigator was reporting on the same clinical problem, and considerably enhance our evaluation of drug therapy.

In the appraisal of drugs intended to alter subjective responses such as head pain, the significance of the placebo deserves specific attention. The role of the placebo in patients with headache is not limited to

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therapy or drug appraisal. It is also useful as a vehicle to determine partially fundamental mechanisms of the actions of drugs designed to modify a subjective response, for considerable evidence has been presented that drugs designed to modify subjective responses do not act primarily on the psychic reaction to pain. Throughout the years, our effective results with placebos, as compared with the drug tested, raised many questions as to the validity of our experimental design and the types of patients we were testing. However, evidence elsewhere has indicated that placebos are increasingly effective with increase in stress. Cleghorn[2] and associates found that an injection of placebo (isotonic sodium chloride) produced a response in patients with severe anxiety similar to that given by corticotropin (ACTH) in normal patients. Using objective laboratory tests, he showed that placebos can stimulate the adrenals and mimic drug action. It also should be emphasized that, in any given situation, responses to a placebo may vary, as compared with any other situation. The individual's attitudes and reactions to treatment vary enormously within each patient and from patient to patient, and cannot be precisely duplicated.

Approximately 90 per cent of the patients who seek a doctor's advice because of a major complaint of headache have vascular headache of the migraine type, muscle tension headache, or a combination of these. The majority of these headaches are the muscle tension type.

Clinical Use of Pharmacotherapy

Headache therapy falls into two categories: (1) symptomatic, or treatment of the individual attack of headache; and (2) prophylactic, designed to prevent or reduce the frequency and severity of recurrence. The goals of pharmacotherapy are to interrupt the mechanism producing pain, to raise the pain threshold, and to reduce emotional stress and anxiety responsible for or associated with the pain.

Muscle Tension Headache:

Tension headaches have no prodroma, are usually bilateral, occipital, or frontal, or even band-like. Frequency and duration are variable, but these headaches commonly last days or weeks. Patients with tension headache describe their symptoms in various ways, including pressing, tightness, generalized head discomfort, or a feeling of wearing a tight cap (hatband type). This type of headache is not pulsatile nor as intense as migraine.

Examination reveals tense muscles and tender spots in the neck and scalp. Movement of the neck may also be limited. Tension headache is not accompanied by neurological signs.

Although the cause of muscle tension headache is not known, there is relatively good evidence that such headaches are related to psychologic disturbances. In patients we have studied, the fundamental psychic factors were sometimes unconscious, although most patients were aware of their anxiety. Headache may also be brought on by economic, social, or physical environmental demands that are beyond the capacity of the patient's abilities. In cases of tension headaches, as in migraine, the most frequently observed conflicts were those related to intense destructive, hostile, and aggressive impulses. Some believe that the psychologic difference between the patient with migraine and the one with tension headache is only the degree of conflict. However, in migraine, additional psychic mechanisms may be operative.

Faulty posture may be a factor in tension headache. As Barlow[3] has pointed out, behavior, as much as structure, determines the mechanics of the body. A person expresses his emotional attitudes by his posture, and muscular tension is part of his defenses. Such results of faulty posture as excessive, sustained muscle contraction in the neck, scalp, and face may cause headache. Some persons may have similar postural attitudes during sleep, which may account for headache being frequently experienced on awakening.

Mechanism:

Sustained contraction of the skeletal muscles of the scalp and neck is usually considered to be the source of the discomfort in tension headache. Electromyographic observations have indicated that procedures that increase action potentials

produce pain and, conversely, those that diminish the potentials decrease pain.[4] It also has been suggested that ischemia may be an added factor producing pain in muscle spasm.[5] Another factor may be central spread of the excitatory effect of noxious stimulation of the nerve endings in the soft tissues of the neck. Whether one or more of these factors is responsible for the pain in muscle spasm is still to be determined. Frequently, an element of tension headache is present during certain phases of the migraine attack, and patients may pass alternately from one state to the other.

Symptomatic Treatment:

In the treatment of an acute attack of severe persistent tension headache, the fact that we are treating not only the perception of pain but the reaction to pain, is well illustrated (Table I and II). As ordinarily used, the non-addicting analgesics alone are seldom effective. Likewise, tranquilizers and sedatives rarely control the discomfort of severe or persistent headache. However, when the analgesic is combined with a tranquilizer or sedative, the combination is effective in the symptomatic treatment of tension headaches.[6] A combination of analgesic, sedative, and/or tranquilizer gives relief in over 70 per cent of treated cases, whereas non-narcotic analgesics or sedatives, when used alone, are less effective (55 per cent). It should be noted that placebos are effective in approximately 45 per cent of these patients.

The ideal analgesic in the treatment of muscle tension headache patient should have the following characteristics: (1) absence of impairment of sensorium or vital functions; (2) absence of addicting properties; (3) negligible side effects or toxicity; and (4) simplicity of administration. No known non-narcotic analgesic fully meets all of these requirements. Although many substances have been synthesized and tested, the most practical and useful non-narcotic analgesic available for head pain of low intensity remains acetylsalicylic acid.

TABLE I

Muscle Tension Headache

Symtomatic Treatment

Medication	*Action*	*% Improved*	*No. of Patients*
Dextropropoxyphene hydrochloride	Analgesic	58	120
Aspirin	Analgesic	55	120
Placebo		45	100

TABLE II

Muscle Tension Headache

Medication	*Action*	*% Improved*	*No. of Patients*
Aspirin Phenacetin Caffeine Sandoptal	Analgesic Analgesic Stimulant Sedative	74	400
Dextropropoxyphene hydrochloride Aspirin Phenaglycodol	Analgesic Analgesic Tranquilizer	69	262
Placebo		45	100

Prophylactic Treatment:

Preventive treatment of tension headaches by chemical agents has undergone a change in recent years because of the introduction of tranquilizers and related compounds. However, since tension headaches are frequently the result of psychological factors, therapy should include this important area. It must be emphasized, however, that drugs cannot replace insight and understanding of one's emotional problems. They are of value in reducing emotional stress and allow the patient to handle these situations more effectively.

For our purpose, tranquilizers can be classified according to chemical structure into four classes of compounds. These are the phenothiazines, the Rauwolfia group, the diphenylmethanes, and substituted propanediols.[7] Members within each chemical group share similar pharmacological properties with other members of the group and often differ from one another only by dosage requirements.

The dosage of these drugs is highly individualized. Some patients respond to small doses of a drug; others need much more. Therefore, determination of the adequate dosage range and the proper dosage which can be adapted to the patient's condition become of paramount importance. A drug should be discontinued if the patient does not respond within one month. In general, our observations indicate that the patients who do not respond

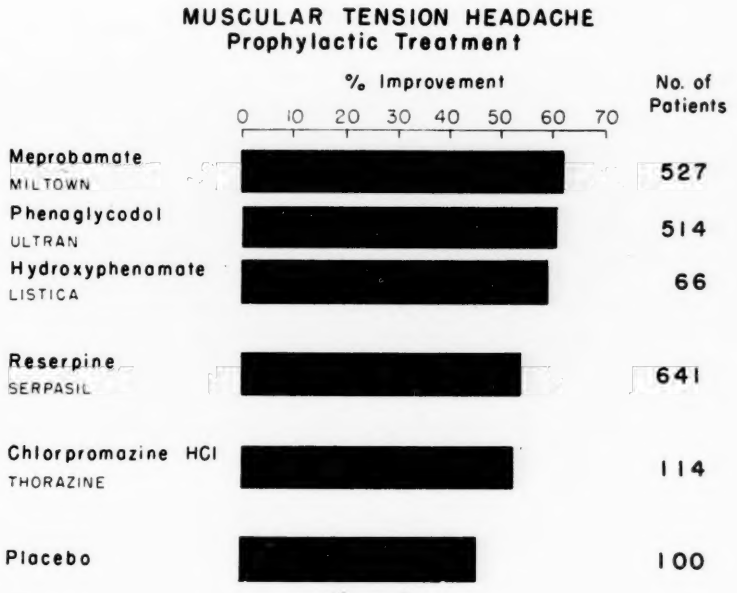

Figure 1

to one tranquilizer also do not respond to another drug of this type. The importance of proper physical and mental examinations in patients receiving these drugs is obvious, for the drugs are capable of producing both physical and mental symptoms.

A new tranquilizer, hydroxyphenamate (Listica), was studied for its effectiveness in the treatment of muscle tension headaches. Sixty-six patients were given hydroxyphenamate over a period of eight months. The majority of the patients were female. The ages ranged from 21 to 65 years, with the majority between the fourth and fifth decade. The average maintenance dose was 600 to 800 mg. daily. The drug was well tolerated and side effects were minimal, in that three patients complained of drowsiness, two of dizziness, and one of nausea. There was no evidence of blood dyscrasias, skin eruptions, jaundice, or addiction.

TABLE III

Hydroxyphenamate (Listica) in Prophylactic Treatment of Muscle Tension Headache

	% *Patients*	*No. Patients*
Improved	59	39
Unimproved	41	27
Total	100	66

In this study, the patients were rated as improved or not improved. The term improvement was used to denote complete freedom from headaches or a significant decrease in their frequency. Improvement was noted in 59 per cent of this group of 66 patients (Table III). These results compare favorably with other tranquilizers used in the treatment of muscle tension headaches (Figure 1).

Our preliminary observations would indicate that this drug is a useful oral medication for prophylactic treatment of muscle tension headache. However, further appraisal of the effectiveness of this compound is necessary before final evaluation can be made. This now is being done with controlled double blind studies.

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DISCUSSION OF DR. FRIEDMAN'S PAPER

Dr. Dorfman: Dr. Friedman provided his own comments by suggesting that the drug alone is not the complete answer, that we had to study the patient longitudinally. The point I would like to make is that these new drugs, whether Listica or any other, offer an unusual opportunity to explore the possibility of biochemical roots in emotional and mental illness. All the answers are not in as yet, but it seems to me that we have to think in these terms: that the brain is not just a chemical box or test tube where you put one drug in and precipitate something else out; neither is it a metaphysical soul. We need a correlation of psychodynamics and psychopharmacology just as we need a correlation between body and mind.

This has repeatedly been pointed out. It has been shown that, in the treatment of patients, you are treating people with organic disease, or let's say non-psychiatric disease, and as I suggested earlier, goals here are different from those of the psychiatrist. In treating a patient with a headache we are trying to prevent headaches and not attempting a radical dissection of the personality. It is true, as Dr. Friedman points out, that the drug alone is often not enough. Let us not fall into a trap of feeling that hydroxyphenamate or any other pill is going to solve all the problems of this world. In most instances these drugs (hydroxyphenamate too) have been useful in improving the communication between doctor and patient. If you have patients who are less anxious and less depressed, you can help them to solve their problems faster.

Moderator: I want to bring up a difficult question while our neurologist-psychiatric friends are here. We have a well known dictum in psychiatry. It is, if you take the symptoms away from the patient you sometimes don't do the patient a service. I thought some of that was present in what Dr. Friedman was saying and I thought some of that was present in Dr. Cahn's statements and certainly in Dr. Alexander's exposition. Would you make a few psychiatric comments?

Dr. Dorfman: I certainly will agree. As I mentioned before I have spent most of my professional life as an internist and became involved with metabolic problems which included patients with obesity. As I grew older, I found more patients that I felt should not be "cured." When I was much younger, I had written a book called "Overweight Is Curable." I wish I could recall this book because I have now learned that you cannot cure all overweight people. When you take away their food (or their headache or angina or pseudo-angina) you are taking away a defense which loss can precipitate something else, especially a psychotic break. I have, on occasion, seen patients with obesity, treated by well-meaning internists, nutritionists and anaylsts, who went into acute schizophrenia by too insistent an attempt to remove this need to overeat. Of course, the life insurance companies point out that overweight is dangerous, and this is true, but everybody cannot be the perfectionistic image that he likes to be. Sometimes it is better to settle for twenty pounds heavier than to spend a life in a mental hospital.

A Double Blind Study Involving Listica, Librium, and Placebo as an Adjunct to Supportive Psychotherapy in a Psychiatric Clinic

BLAINE E. MCLAUGHLIN, M. D.*, JAMES HARRIS, M. D.†, and FRANK RYAN, A. M.‡

The purpose of this study is to evaluate the use of a new psychotropic agent in an out patient clinic, using the patient as his own control with a double blind technique. The psychiatric patient clinic of Woman's Medical College was selected for the study. The Wednesday afternoon clinic consists of about 100 patients, many of whom have been attending regularly since World War II. The patients are comprised mostly of ambulatory schizophrenics, chronic neurotics, and character disorders who are using the clinic as a means of remaining functional in the community. Among them are housewives, domestics, tradesmen, non-skilled workers, and a few adolescents. Many of them have had past hospitalizations for mental illness. They are usually referred by other clinics in the hospital, or local general practitioners and social agencies. The staff consists of only one psychiatrist (Blaine E. McLaughlin) and a secretary. The patients are seen weekly, every two weeks, every month, or every three or four months, and each interview lasts fifteen minutes. Supportive psychotherapy, reassurance, counselling, and maintenance doses of psychotropic drugs are used, and social service and psychological facilities are rarely or infrequently employed. A very small fee is charged each patient. Although some of the patients remain inadequate with tenuous adjustments, only three patients from the clinic required hospitalization in 1960.

For years the psychiatrist has been concerned with the problem of the double blind, and his own therapeutic attitudes. With the introduction of new agents designed for use in mental illness, it has become imperative that adequate methods of evaluating new drugs for clinical use be standardized. The double blind method is designed to help control bias, and the attitudes of the patient and the therapist toward the drug. Gafoulds[1] in 1958 reviewed 36 papers from the British, and 36 papers from the American literature and found that 44% of British drug studies used controls, while only 11% of the American drug studies did so. In those studies which used controls, only 19% of the authors claimed successful results with the drug studies, while in the uncontrolled studies, 85% of the authors claimed success. Modell Houde[2], in a study of double blind technique stated, "it is our categorical stand that, in addition to the use of placebo control, the double blind control should also be used whenever and wherever it is feasible. We conceive of no disadvantage in the application of the double blind control — only protection against spurious data. It does not handicap design or reduce sensitivity, but it must be used to deal with bias and psychic factors which cannot be eliminated."

Thirty-three patients were selected for this study; 22 females and 11 males aged 14 to 70, representing a typical cross-section of the clinic population. Twenty-four patients completed the entire study, and only these patients are reported. Six of these went through the study more than once, but only the first study is reported. Identical bottles of Listica, Librium, and an inactive placebo, all in identical tablet form, were employed in the study. Each bottle had a different number on it, and a coded list was kept in the Hospital pharmacist's safe to be used in the case of a severe reaction to the medication. At no time did the psychiatrist or the pharmacist know the identity of the tablets, or the order in which they were given to the patient. As each patient began the study, he was evaluated by the psychiatrist, and given a bottle with a number on it in a pre-determined se-

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quence. The patient took the tablets t. i. d. and returned in two weeks for an evaluation. He was then given a second bottle, with a different number, and the process was repeated. Thus, each patient was on each of the two active drugs and the placebo for two weeks, a total of six weeks, and was seen a total of four times by the psychiatrist. The Listica was given in doses of 200 mg. t. i. d and the Librium 10 mg. t. i. d. We thus see that while the double blind technique was followed strictly, each patient was treated in exactly the same manner, and the therapist knew that he was actively treating each and every patient. By using this modification of classic double blind, I feel we could take a more positive therapeutic approach in our psychotherapeutic technique.

The evaluation of the patients during the study was made on the basis of social adjustment, and acute symptom relief. No attempt at complete dynamic formulation, depth therapy, or insight therapy was made. If the patients were approaching the optimum adjustment before the onset of acute symptoms or severe social difficulties, the responses were adjudged favorable. The evaluations were grouped into:

Excellent: Striking remission of such symptoms as acute anxiety, depression, suicidal thoughts, and hallucinatory phenomena, and an expression by the patient that he was feeling fine, with general social adjustment improved.

Good: Some remission of the above symptoms, with good social adjustment.

Fair: Temporary or minor remission of acute symptoms with no change in social adjustment.

Poor: No change or worsening of symptomatology and social adjustment. For statistical purposes, fair and poor were considered together.

Results

At the conclusion of the study, the records were decoded. The results were subjected to statistical analysis (Frank Ryan), and only after this was done did the psychiatrist know in which order the drugs had been given. The results are summarized in Table I. As can be seen, there was a significant difference in the responses to the active drugs and the placebo, although there was no significant difference between the two active drugs.

TABLE I

Patient Response to Listica, Librium and Placebo

	Listica	*Librium*	*Placebo*
Excellent	9	8	4
Good	9	11	5
Fair and Poor	6	5	15
Total Patients	24	24	24

$X^2 = 11.718$

Sig = 0.02 level

This study indicates that active psychotropic drugs are effective when used in conjunction with supportive psychotherapy in a clinic as described above. The study did not test the use of the drugs alone, or in conjunction with insight therapy. Since there seems to be a great need for such clinics in the Philadelphia area, the use of such drugs as an adjunct to superficial follow-up therapy seems valuable.

Summary

In a small weekly psychiatric clinic devoted to supportive superficial psychotherapy, a double blind study on Listica, compared with Librium and an inert placebo, showed Listica and Librium to be significantly beneficial in maintaining or improving social adjustment, and in relieving acute symptoms.

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DISCUSSION OF DR. HARRIS' PAPER

WILFRED DORFMAN, M. D.

I thoroughly agree with Dr. Harris' observations concerning a need for clinics and orientations of this sort in psychiatry. Unfortunately it is not prevalent. I might say that I, too, am faced with this dilemma in Brooklyn, which is famous for many things. One thing for which it is infamous is the tremendous division between the so-called analytically-oriented psychiatrist and the internist. I had a double dose because I'd been an internist first, which made me twice as vulnerable. I run such a clinic at the Maimonides Hospital in Brooklyn, where I try to teach medical students how to use these newer psychotherapeutic drugs. This is the way they learn psychiatry. I don't call it psychodynamics, but if you teach a doctor how to use a

drug, when to use it and point up the limitations, you have to bring in the dynamics of the patient.

I joined this clinic just a year ago to find out if these drugs work in a setting of a general hospital, as I know they work in a state hospital. I do know that you can't solve problems with drugs. I know there are plenty of patients in the state hospitals who have had social recoveries with the help of drugs. I also know that the doctor who treats his patients with coronary disease will try to get them back to work in three months or so. He hasn't re-educated the coronary arteries, nor has he resolved the arteriosclerosis, but the fellow is alive. He might get another attack in a year or he may not get one for twenty years.

I think it's about time that we as psychiatrists began to think along these lines, especially for the type of patient who will not accept psychotherapy.

You might try to sit with this type of patient for fifty minutes because that's the way it's taught. Well, some people just can't sit and talk for fifty minutes. Some get worse. There will be others who will not leave and who would keep talking, if the doctor would permit it, for two or even three hours. I think Dr. Cahn's method is the only way to prove these drugs, because in this type of study the doctor functions as a doctor. He can evaluate the drug without psychotherapy, and this is of value in that it can eventually filter through to reach the non-psychiatrist. This is the problem that we are facing today. Only 4% of the doctors in the country are psychiatrists; emotional illness is on the increase. It probably always has been pretty high, but people have denied it. They are becoming more aware of it, and more willing to do something about it, but every good psychiatrist is busy. Now this is quite a problem, gentlemen, because these patients need help and the average non-psychiatrist feels that he doesn't know enough to be of help.

In this type of setting the drug has shown its efficacy. These are the effects that we need to produce social recoveries. We can't change schizophrenia but can often obtain a social recovery, just as with the person with coronary disease who returns to work. These are the goals that may have to be used for certain people, especially ambulatory schizophrenics. This does not apply to the person with an anxiety state who has problems that have to be solved. Pills do not solve problems; they have to be worked through, but some patients can be reached better by combining drugs with psychotherapy.

Clinical Trial of Hydroxyphenamate (Listica) in Alcoholic Patients

C. GOULDMAN, M. D.*, F. LUNDE, M. D.†, and J. DAVIS, R. N., B. A.‡

The management of a large number of alcoholic patients with poor motivations for psychotherapy offers many problems — one among these being the use of medication as an adjunct for relieving tensions, anxiety and hostility and thus obviating their need for alcohol. Attempts at replacing their dependency on alcohol with a psychological dependency on drugs are often more successful than complete denial of their dependency needs; often it is a question of choosing the "lesser of two evils". Addiction to drugs is a possibility in achieving this goal, however, and should be prevented. A wide variety of drugs have been tried for this purpose but none have been found to be consistently effective.

This report is of a pilot study in which the value of a new drug, hydroxyphenamate (Listica), was assessed when used as an adjunct in the treatment of alcoholic patients.

Material

The patients for this study were 39 males admitted to the hospital for the first time because of various personality disorders. These were mainly of the passive-aggressive type, in which excessive drinking of alcohol was considered the primary symptomatic expression. All were from rural and small town locales in the Midwest and ranged in age from 23-61 years (averaging 42.8 years). They had been drinking to excess for an average of 15 years. The routine psychological, physical, neurological, and laboratory work-up did not reveal the presence of any psychoses, severe damage in the general brain functioning, or significant physical deterioration.

Method

The study was carried out in two parts; the first was an evaluation of the effects on 23 consecutively admitted patients who were given 1 tablet (200 mg.) 4 times daily for an average period of 16.78 days. The second part was an evaluation of the drug's effects on 16 patients, using the double blind method. Criteria as to individual improvement were based upon the patient's subjective feeling (stated by the patient as "feeling better", "less tense", etc.); the observations of the ward personnel (patient sleeping better, more sociable, able to discuss problems); and the observations of the ward doctors (more receptive to therapy and able to discuss problems, more outgoing and sociable, etc.).

During the study they were closely observed in order to detect possible side effects. White blood counts were done weekly; other laboratory studies were ordered when indicated.

After an initial sobering-up and observation period, the patients were transferred to a 20 bed ward. The patient program was group-centered and scheduled for a minimum of four weeks. The general program consisted of:

1. Half-day work assignment in the morning.
2. 5 hours weekly group therapy with senior staff members.
3. 2 hours weekly ward meeting with ward aides.
4. Individual supportive psychotherapy of differing intensity.
5. 1½ hours weekly occupational therapy.
6. 3 weekly A. A. meetings, held on the ward and with the group in town.
7. 2 films on alcoholism weekly.
8. 2 hours weekly lectures, discussing the most pertinent problems didactically.
9. They received an adequate, balanced diet with vitamin supplements.
10. Visiting with relatives and friends was encouraged throughout.

Results

First Study — Hydroxyphenamate Only:

This group consisted of 23 male alcoholics with an average age of 42.1 years (ranging from 23-59 years). The following main changes were noted by the patients and reported to the ward personnel and Re-

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search Nurse; 12 patients felt calmer and less tense; 8 patients slept better; 7 patients reported less tremors and less sweating. Seven patients appeared to be more sociable, according to ward personnel. The only side effects occurred in five patients who reported drowsiness which disappeared with a reduction in dosage.

The statistical breakdown of results as determined by the ward doctor was as follows:

	No Pts.	*%*
No improvement	7	30.5
Slight improvement	3	13.0
Moderate improvement	9	39.2
Marked improvement	4	17.3

Although no correlation could be made, there was a fairly marked difference in the personality pattern of the improved versus the unimproved patients. Those who reported no improvement were more defensively hostile, tending to deny their problems and detach themselves in their interpersonal relationships. Some were individuals with rather compulsive personalities. Those who reported improvement tended to be more anxious, depressed, insecure, dependent individuals who responded positively to many attempts to help them.

Second Study — Double Blind Study:

This group consisted of 16 male alcoholics with an average age of 43.6 years (ranging from 23-61 years). One patient escaped and did not complete the study. Of the 7 patients who received both drug and placebo, 3 noticed no improvement and 4 patients stated that they "felt better, more at ease, less tense, and slept better" while on drug. There were only three who complained of drowsiness. Four patients received only hydroxyphenamate; all of these reported that they felt more relaxed and slept better, and they became more sociable and talkative in groups. Two patients complained of drowsiness. Four patients received only placebo — two noted that they felt better, were more relaxed and slept better — whereas the other two remained restless and jittery.

Of the total of 11 patients taking hydroxyphenamate in this study, 8 patients felt better (74%), 3 reported no change (26%), and five complained of drowsiness. Of the 4 patients on placebo, 2 reported that they felt better (50%). No clear cut correlations between improvement and drug effect could be established.

Side Effects

Aside from the drowsiness which was reported in 10 of the 39 patients, there were no side effects.

Summary

In general, all tolerated the drug well and liked the effects obtained while on hydroxyphenamate. The only complaint of the patients was of drowsiness. Eight of the 39 patients on both studies asked for the drug to take with them when discharged, and two still contact the hospital when additional medication is needed. Results were sufficiently encouraging to warrant all patients being placed on the drug when admitted to this treatment ward. Follow-up care was not considered adequate, for unless readmitted, there is no further contact with the patient after discharge. To date, only one patient has been re-admitted.

Summary of Results with Listica in Alcoholic Patients

	No. Pts.	*% Pts.*
Total patients	39*	
Received Listica	34**	
Improved	24	70.6
No change	10	29.4
Received placebo	4	
Improved	2	50.0
No change	2	50.0

* 1 patient escaped and did not complete study.
** 10 patients (29.4%) reported drowsiness.

Discussion and Conclusions

The small size of the groups in the initial study limited the number of conclusions that could be drawn from these findings. The absence of serious side-effects and the patients' preference for hydroxyphenamate was sufficiently encouraging to warrant further investigation. Essentially the same results have been noted in 95 patients who have taken hydroxyphenamate since completion of the pilot study. Further evaluation is being planned in which controlled studies will be carried out in 100 patients to compare the effectiveness of hydroxyphenamate with that of three other drugs.

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DISCUSSION OF DR. LUNDE'S PAPER

Moderator: Would Dr. Rhoades make just a few comments on this paper from the standpoint of the general practitioner? Dr. Rhoades.

Dr. Rhoades: I'd like to point out that the problem presented by Dr. Lunde is a very pressing one, particularly in our large metropolitan areas. In Detroit, perhaps 20 per cent of the patients we see in general practice have some type of alcoholic problem. Obviously, the medication that we use is only part of the treatment. We are dealing with the same problem here that we have in obesity or in many other personality defect problems. We attempt to rehabilitate the patients and redirect their motivation so that we can find an acceptable and nontraumatic substitute for the alcohol in order to effect a cure. This, of course, is difficult; the same is true of obesity. This morning one speaker said that he had written a book on how obesity could be cured and, of course, you could also write one on how to cure alcoholism. In the same sense you can never cure it, but you may in a way teach the patient to control it. Obesity or alcoholism, it is part of the same problem, the person's inadequacy to face life's situations.

Use of Hydroxyphenamate (Listica) in Dermatologic Therapy

MILTON M. CAHN, M. D.* AND EDWIN J. LEVY, M. D.*

Psychosomatic factors play a prominent role in the pathogenesis of many dermatological diseases. In some they are considered to be of primary etiologic significance, while in others they are a concomitant factor which tends to prolong and intensify the clinical expression of the disease. The tranquilizing drugs would seem to be a logical method of therapy in these cases. Accordingly, this study was undertaken to evaluate the effectiveness of hydroxyphenamate (Listica) in the management of many of the dermatoses which are either initiated or perpetuated by unresolved emotional conflicts.

Method

Eighty-five patients who suffered from chronic dermatologic diseases which were considered to have psychosomatic factors playing a role in their pathogenesis, were selected for inclusion in this study. Listica was administered in dosage of 600-800 mg. per day, divided into doses of 200 mg. Clinical observations were made at weekly intervals. Drug administration was continued until the investigators felt they had adequately evaluated the patient's response to therapy. No other systemic medication was administered.

Local (topical) therapy in the main was limited to soothing baths and compresses, and emollient creams and lotions. Thus any definite change in the patient's condition might be correlated, in part at least, to the action of Listica. However, no statistical significance can be inferred from the results because no control group was similarly evaluated.

Results

Eighty-two of the eighty-five patients included in this study took Listica in the prescribed daily dosage for periods of time from two to six weeks. The other three subjects were removed from the study because of side effects attributed to the medication.

TABLE I

Number of Weeks of Therapy

Total number of weeks	*Number of patients (Total 82)*
2	10
3	38
4	29
5	4
6	1

Early in the study it became apparent that proper evaluation of the effectiveness of treatment required two separate standards, and that, in many patients, there was no direct correlation between the two. Thus, results are tabulated in two categories: Table II is an evaluation of subjective improvement as determined by careful questioning along such lines as: "How do you feel?", and "How does your skin condition seem to be doing?" Table III is an objective evaluation of changes in the patient's skin disease, as determined by the investigators.

TABLE II

Subjective Response of Subjects

Diagnosis	*Excellent*	*Good*	*Fair*	*Poor*
Neurodermatitis (generalized) (16)	6	6	3	1
Neurodermatitis (localized) (13)	1	7	3	2
Nummular Eczematous Dermatitis (16)	3	6	3	4
Atopic Dermatitis (9)	1	6		2
Psoriasis (7)		3	1	3
Seborrheic Dermatitis (1)				1
Alopecia Areata (2)		1		1
Neurotic excoriations (5)	2	2		1
Acne Vulgaris (6)	1	4		1
Chronic urticaria (3)			2	1
Pruritus vulvae (2)			1	1
Pruritus ani (2)		1		1
Totals (82)	14	36	13	19

Side Reactions:

No serious reactions occurred. Four patients complained of drowsiness. In none of them was it necessary to discontinue the drug. In one subject, the drowsiness was disabling while taking 600 mg. per day, but

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was relieved when total daily dosage was reduced to 400 mg. In the other three, drowsiness was mild and required no adjustment of medication.

TABLE III

Clinical Response of the Skin

Diagnosis	*Excellent*	*Good*	*Fair*	*Poor*
Neurodermatitis (generalized) (16)	2	3	6	5
Neurodermatitis (localized) (13)	1	6	2	4
Nummular Eczematous Dermatitis (16)	1	4	3	8
Atopic Dermatitis (9)		3	2	4
Psoriasis (7)			2	5
Seborrheic Dermatitis (1)			1	
Alopecia Areata (2)				2
Neurotic Excoriations (5)	1	2	1	1
Acne (6)		2	1	3
Chronic Uticaria (3)			3	
Pruritus vulvae (2)			2	
Pruritus ani (2)			1	1
Totals (82)	5	20	24	33

Three patients became depressed, to a degree severe enough to discontinue medication within the first week of treatment. This symptom promptly disappeared, when medication was stopped.

Discussion

The results of therapy with Listica were classified by (a) objective evaluation of the improvement in the skin condition; and (b) subjective evaluation of the changes in the patient's sense of well being, his attitude toward his skin condition, and the degree of relief of his underlying anxiety. A number of significant points were brought out by tabulation into these two separate categories.

Results classified as "fair" were not considered of significance in a study such as this where no controls were used. "Excellent" and "Good" results were grouped together and seemed to indicate a reasonable degree of improvement which might be ascribed to the action of the drug, since no other specific treatment aside from Listica was employed.

Fifty patients (61%) were subjectively benefited, although only twenty-five patients (31%) had "excellent" or "good" improvement in their dematological disease.

TABLE IV

Comparison of Subjective vs. Objective Responses

	Excellent	*Good*	*Fair*	*Poor*
Subjective	14	36	13	19
Objective	5	20	24	33

Most of the patients whose skin condition improved, also were subjectively better. However, it is gratifying to find that another 25 patients in this series were considerably more comfortable, less tense, and less preoccupied with their dermatoses even though the clinical course of their disease was not significantly improved. It is of interest that the five patients in this series who had "excellent" improvement in the clinical response of their skin disease, also had "excellent" improvement on subjective evaluation. A reanalysis of these cases indicated a common denominator. On clinical observation, these five patients had been more actively agitated and visibly more hyperactive than the other subjects in the study.

Summary

A new tranquilizing drug, Listica, was administered to 85 patients with dermatoses in which emotional factors were considered to play a prominent role either in the causation or the prolongation and intensification of their disease.

Fifty subjects had definite improvement in their sense of well being, relief of underlying anxiety, and in their attitude toward their dermatologic problem.

Twenty-five of these subjects also had substantial improvement in their skin condition.

Dramatic dermatologic and psychogenic improvement occurred in five patients who had been actively agitated and hyperactive.

Four patients noted drowsiness, but not severe enough in degree to discontinue medication. Three patients became depressed while taking Listica. This symptom promptly disappeared when medication was stopped.

DISCUSSION OF DR. MILTON CAHN'S PAPER

Dr. Taub: In the allergic dermatoses that I have tried, in dermatitis and urticaria, etc., Listica does seem to relieve the need for scratching. At least,

they don't scratch so much. They feel subjectively better from that standpoint. When they don't scratch, particularly in the neurodermatitis group, the dermatitis will subside. And, in that respect, I found Listica helpful in allergic dermatitis.

Dr. Eisenberg: These results compare pretty much with ours. I would like to make a comment on one patient who complained that the drug aggravated her nervousness. My nurse told me later about this because this patient was included in the excellent result skin cases. The nurse remarked that, "Perhaps you aren't use to feeling relaxed, and it was a strange feeling for you. This may be bothering you." The patient said, "Maybe so." For the rest of the month this patient was fine on the drug and when it ran out she asked for more, because she got used to and liked the feeling of relaxation.

Question:

Moderator: What happens to the average patient who has a deviation of symptoms under drugs? What adjustment do they then make?

Answer:

Dr. Levy: I think there is one comment we would like to make about these patients. We are assuming here that these are our general dermatologic results. Actually, these patients have been specifically left untreated except for the particular drug in question. These patients, a good percentage of them, do respond to other modes of dermatological therapy so I think that we shouldn't misinterpret the statistics as given.

The patients that the dermatologist refers to the psychiatrist are those who don't respond to dermatological therapy, over and above those who have been described here, and I think that a good percentage of these patients do well on psychotherapy.

Question:

Moderator: What happens to the patients after they clear up their dermatological disorder? Does their life change in any way? Do they have other symptoms?

Answer:

Dr. Levy: Yes, I think so, depending upon the dermatologic conditions, and especially in those conditions such as neurodermatitis. A pure neurodermatitis group is separated from the atopic dermatitis group which has hereditary background and some allergic background. We find in a pure neurodermatitis that if you treat these patients too vigorously they will develop some other symptoms. We did a series of experiments at one time where we took patients with localized neurodermatitis. We prevented these patients from scratching their dermatitis. We actually put a fixed dressing on patients who had neurodermatitis limited to the knee. We took the dressing off a week or two weeks later and the dermatitis was cured, but the patient's peptic ulcer flared up severely. If we removed the dressing and let him scratch his knees again then his ulcer subsided.

Dr. Dorfman: Neurodermatitis is related to the personality of the patient. After all, neurodermatitis itself can't produce these repercussions psychosomatically when the personality structure of the patient is well balanced. I think this brings out the importance of the proper selection of patients and goes back to the many papers which have pointed out that if you select the right patients you will get good results.

Summaries of Clinical Experiences

J. A. Abbott, M. D.

We were asked to test this drug as an anticonvulsant, and I think Dr. Stamps also did that. Our patients were epileptics and the character of this group is described below.

Our subjects consist of 29 patients equally divided between men and women in ages between the 30's and 40's. The type of seizures (each patient had several kinds of seizures) were 9 petit mal, 12 grand mal, 18 psychomotor. That has been our experience with groups of epileptics. The psychomotors were the ones holding out against medicaments. If a good medicine for psychomotor epilepsy can be produced, it will be the last step in the control of epilepsy.

Side effects were very few. There were four drowsy patients, one with ataxia, one with alexia, one dizzy, one irritable (a child of five years). Blood, urine, and symptoms of liver disorder were negative.

Our maximum dose was smaller than that of Dr. Stamps, six tablets of 200 mg. each per day. In every case this was combined with other anticonvulsants.

There were nine good results, and 16 showed no effect. I was puzzled by this distribution and to my distress learned that all the good results were in patients assessed one year ago. I am afraid that when we reassess results they will move over to the other end of the range, so I suspect that in the long run the compound will not prove an effective anticonvulsant.

(The following summary was received from Dr. Abbott subsequent to the symposium).

Hydroxyphenamate (Listica) was given to 32 epileptic patients, the majority of whom were judged to have idiopathic epilepsy. Data on its effect were inadequate in two cases, leaving 31 cases to be reported. For these 31 patients effectiveness as an anticonvulsant was judged to be good for 2, fair for 1, and poor for 2 patients; it was judged to be without effect as an anti-convulsant for 26 patients.

It was given to patients whose epilepsy had already proven resistent to a large number of other anticonvulsants of established value. By this rigorous test, it appeared to have slight but definite effectiveness as an anticonvulsant. From its slight effectiveness by this test we cannot conclude that it is inferior as an anticonvulsant to the other anticonvulsants of established value with which it was tried and which had themselves proven only moderately effective.

Oscar F. Davis, Ph. D., M. D.

The capacity to attenuate anxiety and induce other behavioral changes is very difficult to evaluate. However, conclusions about psychotherapy, environment or the transitory effect of drugs on behavior can be reasonably reached if they are gleaned from a large, randomized, controlled study group. In accordance with this concept a group of 233 patients of both sexes was studied. The patients evidenced anxiety, present to or associated with, psychosomatic illness.

The group was structured within limits short of obvious and gross psychosis or extreme neurosis. Psychiatric examination was not undertaken, but obvious psychiatric cases were eliminated from consideration of results. This did not seriously mitigate the investigation, since the goal of the study was not therapy, (in a psychological sense) but rather the temporary relief of anxiety in patients burdened by disease.

All patients received one tablet four times a day. Three controls were employed: meprobamate, 400 mg. per tablet q.i.d., APC tablets, and cessation of therapy. The cessation of therapy was undertaken after anxiety had been allayed with reasonable consistency for a period of three days and then anxiety was re-encountered after treatment was stopped. The drug was then re-employed and a second amelioration of anxiety was studied.

A total of 203 patients were treated with hydroxyphenamate, 20 with meprobamate and 10 with APC. The 203 patients had anxiety associated with GI disturbances, cardiovascular-renal disturbances, obstetrical and gynecological manifestations, surgery and metabolic-endocrine disorders. The 20 patients studied with meprobamate had anxiety symptoms associated with GI and cardiovascular disease. The 10 treated with APC were all cardiovascular patients.

In the hydroxyphenamate treated group, virtually complete relief from anxiety was obtained in 69 patients, moderate relief in 85 patients. There was no relief in 34 patients, and in 15 there was an increased anxiety. The results were less favorable for the meprobamate group and still less favorable for the APC treated group. Drowsiness was noted in about 2% of the cases, a slightly higher incidence of drowsiness was noted in the meprobamate treated patients.

The authors conclude that the calming properties of hydroxyphenamate affords a broader spectrum of usefulness than meprobamate. The reliability of consistency of the calming response was considered of a sufficient order to recommend the compound for further clinical application.

Wilfred Dorfman, M. D.

My experience with hydroxyphenamate dates back to November 1960 — a period of seven months. My first study was preliminary in an effort to screen the areas in which it is most effective. This was

done by a double blind crossover technique with each patient receiving coded drug or placebo for two weeks and then switched to the other coded product.

There were 27 patients in this first study and the results were as follows:

1. Fourteen patients did not complete the study.
   a. *Diagnosis:* Schizophrenics (5), pseudoneurotic schizophrenics (2), involutional psychosis (1), depressions (3), hysteria (1), personality disorder (1), and Gilles de La Tourette syndrome (1).
   b. *Reason for dropping out:* Too sick (8), preferred previous medications (3), unmotivated for drug therapy (3).
2. Thirteen patients completed the study.
   a. Four were same with drug or placebo Involutional psychosis (2) and schizophrenia (2).
   b. Nine were better with active drug.
   c. Improvement was noted in the following diagnostic categories:

Psychoneurosis with Anxiety	4
Personality Disorders .. with Impulsiveness or Anxiety	2
Anxiety after ECT lifted Depression	1
Severe Obsessional Neurosis (phobic)	1
Conversion Hysteria (with neck pains)	1
	9

In my second study I used the drug in treatment of six patients concomitant with psychotherapy. All of these patients showed excellent short term results and this drug facilitated psychotherapy. These patients were in the following diagnostic categories:

Anxiety Neurosis	1
Impulsiveness (Psychoneurosis)	3
Phobic state (Psychoneurosis)	1
Conversion Hysteria	1

From my experience in these preliminary studies, it would appear that further study of this drug is warranted in impulsive and phobic states and in psychoneurosis with anxiety.

F. W. Stamps, M. D.

About three years ago Dr. Bastian and Dr. Schultz brought me the preliminary work in animals on hydroxyphenamate, and it looked as if it would be very effective. It had excellent Metrazol and electroshock protection in animals so we were quite enthusiastic in our hopes that this would be a good anticonvulsant drug. In the past three years, I have put almost 70 patients on the drug but I evaluated only 52 because I have an outpatient clinic and some of the patients were lost. Some epileptic patients are unreliable about taking medication and we couldn't evaluate more than 52 cases. Unfortunately, this does not look like a good anti-epileptic drug. It does have some anticonvulsant properties as illustrated in Table I.

TABLE I

Epilepsy	*Percent Improvement of Seizure Control*				
	0%	50%	75%	90%	100%
Grand Mal	5	4			
Psychomotor	11	2			
Gmal and Pmotor	11	5			
Petit-Mal	2				
Pmal and Gmal	3				
Others	7	1	1		
	39	12	1		

All of these patients are severe epileptics. They have all had the usual anticonvulsants in large doses and have had many experimental anticonvulsants. We know what their seizure freqency is because we have followed them for as long as 10 to 15 years. We didn't discontinue any of their drugs, just added hydroxyphenamate. Some patients are still taking 2400 mg. a day in addition to other medication. They may be on 3 or 4 Dilantin, some phenobarbital, Mysoline, etc.

I would not consider this compound a really good anticonvulsant because not a single case has been completely seizure free for three months. We thought one little girl was doing quite well. She went about five months without seizures and then broke through.

The patients that responded best were the grand-mal patients. Petit-mal and grand-mal mixed epilepsy and other kinds of petit-mal mixtures, such as petit-mal variant, failed of any improvement. A Jacksonian case gave us the best response with 75% control of seizures.

I don't want to be the one to disagree about the efficacy of this drug but epileptics are different. What we want to do is to take away their symptoms and the vast majority will not develop new ones. If you can take away the symptoms of seizures in the majority of epileptics, they can get an education or hold a job. In a few epileptics the converse is true; if you bottle up seizures with a drug, and some drugs are worse than others, you can precipitate a frank psychosis, but in almost every case this psychosis is reversible by withdrawing the drug and having the seizures recur spontaneously.

S. J. Taub, M. D.

Emotional factors in anxiety influence and modify various symptoms in allergic diseases. We do not believe that these factors are primary or direct etiologic causes of the ailments, but they may accompany the allergic state as in other prolonged illnesses. Since they act as contributory or associating factors, these symptoms should not be ignored.

Because of these psychosomatic relationships it was natural for the allergist to be concerned with the role of tranquilization in the treatment of the

allergic patient. I have tried a number of tranquilizers currently available, but have encountered various side effects, some serious, that necessitated discontinuing the medication.

The present communication reports on hydroxyphenamate in a series of 70 patients given 200 mg. tablets 3 or 4 times a day depending on the degree of anxiety or agitation. There were 29 hay fever and asthma patients, 14 with urticaria angiodema, 11 allergic rhinitis, or dermatitis and 16 miscellaneous. The length of treatment ranged from 1 to 13 weeks.

Results were excellent and good as shown in Table 1. No untoward reactions occurred in this group except for one patient I did not include who became depressed after taking three or four tablets. He is not included in this report. This same symptom was present when he had taken two other tranquilizers.

It was noted that the hay fever-asthma patients on hydroxyphenamate and particularly the asthma group, responded much better than did those patients on routine therapy without the adjunctive use of the tranquilizer. In the urticaria or allergic dermatitis group, the patients had less pruritis, were not as emotional, and stated they felt more relaxed. Manifestations of symptoms of anxiety, restlessness, and irritability, secondary to an allergic disorder were controlled with complete absence of side effects, except for the instance mentioned. In addition, I found hydroxyphenamate more effective than all other tranquilizers previously prescribed.

TABLE I

Diagnosis	# *Patients*			*Age Range* (yrs.)	*Therapy Range* (wks.)	*Results*	
	Total	*M*	*F*			*E*	*G*
Asthma Hayfever	29	7	22	20-67	2-13	28	1
Urticaria Angio-Edema	14	5	9	12-62	1-12	12	2
Allergic Rhinitis or Dermatitis	11	3	8	19-65	3-12	11	0
Miscellaneous	16	7	9	36-75	1-12	14	2
Totals	70	22	48	-	-	65	5

Dosage — One Tablet 3 - 4 Times Daily

Discussion of Dr. Taub's Clinical Summary

BEN C. EISENBERG, M. D.

Dr. Taub's experience parallels my own with respect to the use of Listica, with the exception of side effects. We were very meticulous, to mark down any complaint the patient had with reference to the drug. Further work with the drug will probably bring out some other side effects but this work with allergic patients shows that actually all medical fields have a need for tranquilizing drugs, especially non-toxic ones. We feel that the patients will, in the long run, benefit, especially from short courses with these medications while we treat them vigorously for their basic conditions.

We should not treat patients for symptom removal alone, as the patient will very often develop other conditions as was mentioned by our discussant of the dermatologic patients treated with Listica. I have in mind two patients who committed suicide because of becoming severely depressed when I attacked their asthma very vigorously some years ago. I kept after these patients until they were free of asthma. One was a 12-year-old youngster, a very bright boy who became quite depressed and whose parents were overly strict, and when he had no asthma, he committed suicide. So symptom removal can be dangerous if the basic problems are not gone into thoroughly. This is true even with the use of hypnosis to remove symptoms. We shouldn't just stop there. Our group has worked with hypnosis and we find that while it is helpful in some allergic cases, we cannot stop with just symptom removal.

A point I discussed with Dr. Alexander should be brought out. This is a matter of allergic conditions occurring in patients after retirement from business. I had a number of cases of asthma in women in their 60's. This asthma came on when the mate retired from active business life, and proved to be due to the fact that the patients, as Dr. Alexander so aptly put it, lost their privacy. They found that they couldn't carry on their regular routine. When they got up they did certain things around the house and attended to cooking in a certain way. As one expressed it to me, "I can't stand that man following me around, breathing down my neck, asking me 'what are you doing now,' 'that smells funny,' 'what do you need to vacuum now,' and that sort of thing." This can really produce asthma in these poor souls. When we eventually get the husbands to see that the women do need their privacy, these cases can very often improve with the help of a tranquilizing drug.

General Discussion

Dr. Dorfman: Dr. McLaughlin describes patients who were all ambulatory schizophrenics. It seems to me, in view of Dr. Alexander's comments and of others and in the few patients I have seen, that if you picked the patients who were impulsive and not apathetic the number benefited might have been a lot larger.

Dr. McLaughlin: I have learned that today and I have learned to focus myself a little better.

Dr. Dorfman: Also, with all the wonderful advantages of the double blind (and nobody can question that this is much better than a non-controlled study), we must remember that the dose remains fixed. This is a point again that I believe Dr. Alexander made with the heavy patient who needs more drugs. This, too, can affect the results. Most important is that these patients were on Listica for only two weeks. What can we expect in this short period of time?

Dr. McLaughlin: I think Dr. Alexander's findings are most helpful to me and I can sharpen my focus now in handling the laboratory schizophrenic, which is a particular interest of mine.

Dr. Alexander: I was in a rather fortunate position. I tried to find out about this happening objectively, as we have controls of repeat tests under other forms of treatment. Test and retest consistency, of course, are not included here in detail except for these two other drugs. Now, what the conditional study shows is that this is a mild drug because it produced disinhibition of differentiation that Russian authors also have found to be the mildest form of drug effect on conditional responses, and it then very gradually accumulated. Perhaps the greatest advantage of the drug is its mildness. There is no other drug that has these effects, except benactyzine. Let's take again these impulsive people who seem to stand out better in this pilot study. They are the people who don't like to have any more drugs. They are the ones who rebel, who after a week or two come back and say, "I can't stand it." Therefore, these people would like the drug to start with and they will stay on it longer. The question somebody brought up that I have been asking myself is, "Do these people have a naturally better prognosis?" I think we should now actually run a study to see how the impulsive people vs. non-impulsive people in all diagnostic categories do on psychotherapy alone. Are they better that way too? In other words, there is no end, once you start to do statistics. It is like taking ticks off a dog, you can never rule out all the aspects, but each time you learn at least one little thing.

It is interesting to note from the studies that there is no tolerance. So, I think these little things will probably stand. It is true, of course, that drugs alone do not do anything in psychiatry; with it always goes a psychotherapeutic interpretation. As a physician, one must handle these patients and interpret to them. I told Dr. Eisenberg that the right kind of interpretation is important. I told him about the lady who broke down after her husband retired. Somebody interpreted this to mean that all these years she hated him and resented him because he had neglected her. As a company sales manager he had to be away five days each week. Now she retaliates and hates him and they were both really down. I interpreted this to them as a loss of privacy and encouraged them, after I got her well very promptly with amitriptyline and a bit of psychotherapy. They both cheered up immediately when I told them that it was not hate but that they needed privacy. I encouraged her to keep up her golf and not always make lunch for her husband. Her husband can make his own lunch and he should go out fishing when he likes. They have been well for over a year.

In another case, the right word is important. The word "trapped" is the magic word in this case. Another woman patient with severe agitated depression was married for 29 years to a man she hated. He was worth every bit of her hatred — their three children confirmed that. She stuck to him and said that when her last daughter married she would divorce him, and she did. Then she married a man who was the sweetest and the loveliest man in the world and sure enough he was every bit of that. Then, six months later she was in a severe state of depression and again she went to a psychiatrist who tried to interpret this to her. He told her, "You had a need to hate," and she was frustrated because she couldn't hate this man. That was a very upsetting interpretation to her. I told her this was different; she always needed a sense of freedom and it isn't that she had a need for hatred. In her first marriage she didn't feel trapped and would say to herself every day that she could leave this man at any time she wanted, so she could stand it and she worked at a very good job. Then she was married to this other man who is very nice to her. She suddenly has the feeling that this is it, you know, "trapped." That did the trick—this appealed to her. We must be careful of these psychiatric cliches, and have a more natural understanding for the patients' need for explanation.

Moderator: I think this was very well taken. Dr. Rhoades, would you like to make further comment?

Dr. Rhoades: I would only like to point out from having had about ten years' experience in the educational efforts of the Academy of General Practice that the one group of specialists that we have

found to be wholeheartedly in accord with our ideas is the APA. Here is a splendid example of specialists who give of themselves unstintingly, and do not purport to claim that what they have is impossible of assimilation by the family physician. Ever since life began, I think man has been searching for Elysian fields and the old story, of course, is of the Lotus Eaters. Today it is of the tranquilizer consumer. The family physician and general practitioner are hunting for the happy pills which they can use liberally with their patients and not worry about blood dyscrasias or other serious side effects. If we had a medication that would fulfill these requirements, we then could tackle the whole host of minor neuroses that the APA would like us to handle.

Moderator: Are there further questions?

Question:

From the floor: What is the biggest dose that has been given?

Answer:

Dr. Stamps: A number of patients are routinely taking 2400 mg. a day. The biggest single dose was taken by a child: she took 20 tablets at one time. She became drowsy, had a little ataxia but that is all. She showed protein in her urine but we didn't have her pre-drug urinalysis. She had only taken the drug a few days and right afterward she went to California.

Question:

Moderator: How about the laboratory data on the patients taking 2400 mg?

Answer:

Dr. Stamps: There are many who have been almost three years on that dosage. Their urinalysis, c.b.c and urinary urobilinogen have all remained normal every month.

Question:

Dr. Lunde: Have you seen any withdrawal symptoms?

Answer:

Dr. Stamps: No, I withdraw slowly as with all anti-convulsants, but no symptoms have been noted.

Moderator: Are there any other comments?

Dr. Alexander: I have seen two cases of hypotension on high doses. On 200 mg. three to four times daily, there was no change in blood pressure in any of the patients.

There were two cases with changes in blood pressure and they were the following:

An epileptic who was already on Mysoline and Dilantin to whom I added 400 mg. Listica four times daily. He had petit mal and psychomotor seizures. For one week he was entirely seizure free. When Listica was reduced to 200 mg. four times daily his blood pressure came back to normal and the psychomotor seizures vanished; only his petit mal remained. He is a very obsessive man and had little symbols for each type of seizure and only the stars representing petit mal remained in his weekly reports. So I must have started him at too heavy a dose.

The other one was a post traumatic headache patient who had occasionally showed blood pressure lower than what I presumed to be his normal. He had been operated on for a subdural hygroma and I gave him 200 mg. four times daily which did not touch his blood pressure but it did not relieve his headache. So I tried to raise it to 400 mg. three times daily and then his blood pressure dropped.

Question:

Dr. Burton Cahn: To where did his blood pressure drop?

Answer:

Dr. Alexander: From 145 to 95/70.

Question:

Dr. Bossinger: Dr. Cahn, didn't you just do a study on 1600 mg. of Listica per day?

Answer:

Dr. Burton Cahn: Yes, I treated 10 subjects for a period of six weeks on 1600 mg. daily. We took daily blood pressure recordings in the sitting position at 4 p.m. daily and got no appreciable change in the blood pressure of the subjects who were treated. In the epileptic patient, it sounds like it's possible that a synergistic effect was established, possible with Mysoline to produce the drop in blood pressure.

The one factor that we have to take into consideration in regard to the blood pressure in the patients who were treated for anxiety is, "what constitutes the normal blood pressure?" Frequently, anxious patients run a higher than "normal" blood pressure, and having been given a tranquilizer which does reduce their level of anxiety, it is not unusual to see a drop in blood pressure to a more or less "normal" range for that particular patient. We do not know what the normal range is because by the time we see them the patient is already anxious.

Dr. Lunde: I would like to add that we have always checked for hypotension. We have not seen hypotension in 230 patients. We have no ataxia either.

Dr. Dorfman: I think we shouldn't overlook the problem of ataxia. We've heard the pharmacologist, Dr. Bastian, explain the lack of ataxia with hydroxyphenamate. Those at the APA last year heard about this fellow from Texas who had an automobile accident after drug therapy. I think it is terribly important to remember that, in our older age group, the causing of ataxia by a drug like Librium might produce difficulties. I haven't seen too many myself but I have read of fractures from this in the older age group, and I think this

is one area where hydroxyphenamate might seem preferable.

Question:

Dr. Bastian: I wonder if Dr. Burton Cahn would compare Listica with the other tranquilizing drugs he has studied, both in regard to therapeutic effectiveness and side effects.

Answer:

Dr. Burton Cahn: While I have not directly compared Listica with meprobamate or Librium. I have run them side by side. It is my impression that, in comparing Listica with meprobamate there was very little difference, either in the side effects which I encountered or with the clinical response. If anything, meprobamate had a greater tendency to produce drowsiness in the subjects treated. With regard to Librium, I think there is quite a major difference. Again, I found that hydroxyphenamate and Librium were equally effective clinically. This is a subjective evaluation because I did not objectively or blindly run this study and then compare results. This is on the basis of patients whose symptoms I've observed. If they don't improve I change their medication. With the hydroxyphenamate patients I have not had to change the medication, as is generally the case with Librium. The one major difference that I find with Librium is that the dose in the individual patient is more variable. One cannot establish that 30 mg., 50 mg., or 60 mg. of Librium is going to treat the patient. One has to titrate the patient. Some people I have treated at 30 mg. and others at 400 mg. The 400 mg. dose was not in a psychotic patient but in a severe obsessive-compulsive, and I think I have used about every dosage rate in between. Again, Librium in its side effects produces drowsiness at one level, but if you continue it and go above it the drowsiness will abate. However, and this is a major difference, if Librium is continued up to toxic levels it will produce ataxia. I haven't had this experience with hydroxyphenamate and I am impressed at the absence of severe side effects that would necessitate stopping the drug. I think it is a safe medication.

Dr. Stamps: I would like to add that I am still using the drug for its tranquilizing effects on my epileptic patients. The explosive episodes that psychomotor patients have (that are not seizures) are benefited.

Listica Clinical Summary

R. A. HECHT, M. D. and J. A. HUBATA, M. D.

Listica has been clinically evaluated in a total of 1155 patients presenting various conditions associated with anxiety or tension. The results obtained are summarized in the following table. It should be noted that the effects observed are referrable to the anxiety-tension component associated with the primary diagnosis.

In summarizing the results, we find Listica to be "excellent" or "good" in approximately 74% of the patients and incorporating the "fair" responses we find the product beneficial in 88% of cases.

Listica, in the dosage recommended, has a very low incidence of side effects. Side effects were noted in only 61 of the 1155 patients evaluated. Of these, 39 were reported as drowsiness. Other side effects, all of minor nature, totaled less than 2% of the cases. There were no reports of habituation, headache, palipitation, dryness of mouth or hypotension, many of which have been reported with other tranquilizers.

Listica is specifically indicated for anxiety-tension states. In our studies to date, it has been notably free of undesirable effects so that it appears to be an ideal drug for the office and clinic treatment of non-psychotic patients. It lends itself as adjunctive treatment in a wide variety of conditions commonly seen in everyday practice.

TABLE I

Effect of Listica on Anxiety-Tension

(Dosage: One tablet three or four times daily.)

		Results				
Diagnosis	*No. of Patients*	*Excellent*	*Good*	*Fair*	*Poor*	*None*
Alcoholism	39	4	24	3	8	0
Allergy	59	21	12	12	14	0
Anxiety-Tension and Neurosis	203	89	83	19	12	0
Asthma	64	41	15	4	4	0
Cardiovascular	142	47	52	29	14	0
Dermatology	215	50	112	27	25	1
General Tensions	29	8	18	2	1	0
Genito-Urinary	6	3	3	0	0	0
Gastro-Intestinal	129	33	56	24	16	0
Headache-Tension	53	7	13	13	20	0
Menopause	35	20	14	0	1	0
Obstetrics and Gynecology	69	36	29	2	2	0
Psychotic	63	14	17	18	14	0
Surgery	33	14	6	5	8	0
Trauma	12	3	8	1	0	0
General	4	0	0	4	0	0
Totals	1155	390	462	163	139	1

(as of 3/21/61)

Symposium Conclusion

BLAINE E. MCLAUGHLIN, M. D.

The papers read today have presented a wide variety of clinical experiences of internists, psychiatrists, neurologists, allergists, dermatologists, and chemists around the focal point of the experimental use of Listica, a new neurolytic agent. My over-all feeling, at this time, is that it is apparent that each man has presented not only a summary of his own professional investigative experiences, but also a part of a mosiac covering a vast area of professional attitudes toward human illness. Each paper has added something to this grand design of how clinical physicians approach the ills of human beings. By limiting ourselves to the focal point of this one drug's therapeutic effects we have been able to exchange our philosophies and treatment ideals across many professional barriers. I feel closer to the allergist and the dermatologist than I did before this meeting. I sense a better understanding of the aims of the internist and the general practitioner. I hope they, too, have been able to identify more closely with the psychiatrist in his aims and ideals for treatment. Let us all remember that we come as physicians interested in the total understanding and care of our patients. This meeting has helped me to better realize that no physician is merely a technician with a stereotyped therapeutic approach. Each is rather a scientist interested in the problem of human illness and alert to the possibility of new and untried attitudes of helpfulness to his patients.

I think we go away from this meeting, not only with a better understanding of the total scope of Listica, but with a better understanding of our own attitudes toward our patients, our colleagues and the pharmaceutical chemists who have opened up new therapeutic vistas.